ステラーラ点滴静注 130 mg
ステラーラ皮下注 45 mg シリンジ
ステラーラ皮下注 45 mg バイアル

に関する資料

本資料に記載された情報に係る権利及び内容についての責任は、ヤンセンファーマ株式会社に帰属するものであり、当該情報を本薬剤の適正使用以外の営利目的に使用することはできません。

ヤンセンファーマ株式会社

1.5　起原又は発見の経緯及び開発の経緯

起原又は発見の経緯及び開発の経緯を主に第 2 部（5）に記載した（表 1.5-1）。また，本申請に関する品質及び臨床試験の一覧をそれぞれ，表 1.5-2 及び表 1.5-3 に示す。

表 1.5-1 CTD 1.5 項の内容の記載場所

CTD 1.5 項の内容	CTD 第 2 部の記載場所
起原又は発見の経緯	2.5.1.1 臨床薬理学的分類及び申請効能又は効果
小児クローン病の臨床的／病態生理学的側面及び治療の現状，並びに本薬開発の科学的根拠	2.5.1.2 開発の科学的根拠
開発の経緯	2.5.1.3 臨床開発経緯
申請効能又は効果に対する有用性	2.5.6 ベネフィットとリスクに関する結論

表 1.5-2 品質に関する試験の開発経緯*

試験項目	試験対象	実施時期
製剤開発/規格及び試験方法	製剤	[redacted]年[redacted]月～[redacted]年[redacted]月
安定性	製剤	[redacted]年[redacted]月～[redacted]

* 本剤の皮下投与バイアル製剤に関する開発経緯である。皮下投与シリンジ製剤及び点滴静注製剤は既承認（承認番号：22300AMX00422000 及び 22900AMX00514000）

表 1.5-3 臨床試験の一覧

相	実施地域	対象	試験番号等	実施時期
1	海外	中等症から重症の活動期クローン病の小児患者	CNTO1275CRD1001（評価資料）	2017 年 1 月～2022 年 3 月
3	国際共同	中等症から重症の活動期クローン病の小児患者	CNTO1275CRD3004（評価資料）	2021 年 4 月～2025 年 3 月
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3001（参考資料）	2011 年 6 月～2013 年 7 月
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3002（参考資料）	2011 年 6 月～2014 年 10 月
	国際共同	中等症から重症の活動期クローン病患者	CNTO1275CRD3003（参考資料）	2011 年 9 月～2019 年 10 月

1.6　外国における使用状況等に関する資料

ウステキヌマブ（遺伝子組換え）は，2008 年 12 月にカナダで乾癬に係る適応で承認されて以降、2025 年 8 月現在、欧米を含む 80 カ国以上で承認されている。「中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）」及び「中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）」を効能又は効果とした小児用法及び用量について，2 歳以上で体重 40kg 以上の小児に対して 2025 年 3 月に欧州で承認されており，2 歳以上で体重 40kg 未満も含めた用法及び用量については米国及び欧州で 2026 年 4 月に承認されている。

次頁に，本薬の企業中核データシート（CCDS）及び米国，欧州の添付文書を添付する。

Janssen Research & Development, LLC

COMPANY CORE DATA SHEET

STELARA® (ustekinumab)
(concentrate for solution for infusion)

(solution for injection)

([redacted] 20[redacted])
VERSION [redacted]

[redacted]

[redacted]	[redacted]
[redacted] mg [redacted]	[redacted]
[redacted] mg [redacted]	[redacted]

非公表のため、以下2～90頁を省略

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Ustekinumab safely and effectively. See full prescribing information for USTEKINUMAB.

Ustekinumab injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	4/2026
Dosage and Administration (2.4, 2.7)	4/2026
Warnings and Precautions	
Infections (5.1)	4/2026
Serious Hypersensitivity Reactions (5.5)	11/2025

----------INDICATIONS AND USAGE----------

Ustekinumab is a human interleukin-12 and -23 antagonist indicated for the treatment of:

- Moderate to severe plaque psoriasis in adult and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy. (1.1)
- Active psoriatic arthritis in adults and pediatric patients 6 years of age and older. (1.2)
- Moderately to severely active Crohn's disease in adult and pediatric patients 2 years of age and older. (1.3)
- Moderately to severely active ulcerative colitis in adult patients. (1.4)

----------DOSAGE AND ADMINISTRATION----------

Adult Patients with Plaque Psoriasis Subcutaneous Recommended Dosage (2.1):

Weight Range (kilograms)	Recommended Dosage
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Pediatric Patients 6 Years of Age and Older with Plaque Psoriasis Subcutaneous Recommended Dosage (2.1): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):

- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Psoriatic Arthritis Pediatric Patients 6 years of Age and Older Subcutaneous Recommended Dosage (2.2): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

Crohn's Disease Initial Adult Intravenous Recommended Dose (2.3): A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	Recommended Dose
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Crohn's Disease Maintenance Adult Subcutaneous Recommended Dosage (2.3): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

Crohn's Disease Initial Pediatric Intravenous Recommended Dose (2.4):

- For patients weighing 10 kg or more: A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	Recommended Dose
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Crohn's Disease Maintenance Pediatric Subcutaneous Recommended Dosage (2.4): The recommended maintenance dosage in pediatric patients using weight-based dosing is:

- *10 kg to 35 kg*: a subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *Greater than 35 kg*: a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

Ulcerative Colitis Initial Adult Intravenous Recommended Dose (2.5): A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	Recommended Dose
up to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage (2.5): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

----------DOSAGE FORMS AND STRENGTHS----------

Subcutaneous Injection (3)

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

Intravenous Infusion (3)

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

Clinically significant hypersensitivity to any ustekinumab product or to any of the excipients in Ustekinumab. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Avoid starting Ustekinumab during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue Ustekinumab until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Consider diagnostic tests for these infections as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with Ustekinumab. Initiate treatment of latent TB before administering Ustekinumab. (5.3)
- Malignancies: Ustekinumab may increase risk of malignancy. The safety of Ustekinumab in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Serious Hypersensitivity Reactions: If a severe or other clinically significant hypersensitivity reaction occurs, discontinue Ustekinumab immediately and initiate appropriate medical treatment. (5.5)
- Posterior Reversible Encephalopathy Syndrome (PRES): If PRES is suspected, treat promptly, and discontinue Ustekinumab. (5.6)
- Immunizations: Avoid use of live vaccines in patients during treatment with Ustekinumab. (5.7)

- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of Ustekinumab. If diagnosis is confirmed, discontinue Ustekinumab and institute appropriate treatment. (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Psoriasis and Psoriatic Arthritis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease in Adults
  - induction (≥3%): vomiting. (6.1)
  - maintenance (≥3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)
- Ulcerative Colitis in Adults
  - induction (≥3%): nasopharyngitis. (6.1)
  - maintenance (≥3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Plaque Psoriasis (PsO)
- 1.2 Psoriatic Arthritis (PsA)
- 1.3 Crohn's Disease (CD)
- 1.4 Ulcerative Colitis (UC)

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosage in Plaque Psoriasis
- 2.2 Recommended Dosage in Psoriatic Arthritis
- 2.3 Recommended Adult Dosage in Crohn's Disease
- 2.4 Recommended Pediatric Dosage in Crohn's Disease
- 2.5 Recommended Dosage in Ulcerative Colitis
- 2.6 General Considerations for Administration
- 2.7 Preparation and Administration of Ustekinumab 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease and Ulcerative Colitis)

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Infections
- 5.2 Theoretical Risk for Vulnerability to Particular Infections
- 5.3 Pre-treatment Evaluation for Tuberculosis
- 5.4 Malignancies
- 5.5 Serious Hypersensitivity Reactions
- 5.6 Posterior Reversible Encephalopathy Syndrome (PRES)
- 5.7 Immunizations
- 5.8 Noninfectious Pneumonia

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Concomitant Therapies
- 7.2 CYP450 Substrates
- 7.3 Allergen Immunotherapy

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Adult Subjects with Plaque Psoriasis
- 14.2 Pediatric Subjects with Plaque Psoriasis
- 14.3 Psoriatic Arthritis
- 14.4 Adult Crohn's Disease
- 14.5 Pediatric Crohn's Disease
- 14.6 Adult Ulcerative Colitis

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis (PsO)

Ustekinumab is indicated for the treatment of adults and pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

Ustekinumab is indicated for the treatment of adults and pediatric patients 6 years of age and older with active psoriatic arthritis.

1.3 Crohn's Disease (CD)

Ustekinumab is indicated for the treatment of adults and pediatric patients 2 years of age and older with moderately to severely active Crohn's disease.

1.4 Ulcerative Colitis (UC)

Ustekinumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Plaque Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dosage is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dosage is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

In subjects weighing more than 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these subjects *[see Clinical Studies (14)]*.

Subcutaneous Pediatric Dosage Regimen

Administer Ustekinumab subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of Ustekinumab for pediatric patients 6 years of age and older with plaque psoriasis based on body weight is shown below (Table 1).

Table 1: Recommended Dose of Ustekinumab for Subcutaneous Injection in Pediatric Patients 6 Years of Age and Older With Plaque Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

For pediatric patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the vial.

Table 2: Injection Volumes of Ustekinumab 45 mg/0.5 mL Vials for Pediatric Patients 6 Years of Age and Older With Plaque Psoriasis and Pediatric Patients 6 Years of Age and Older With Psoriatic Arthritis* Weighing Less Than 60 kg

Body Weight (kg) at the Time of Dosing	Dose (mg)	Volume of Injection (mL)
15	11.3	0.12
16	12	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43

53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

* Refer to 2.2 Psoriatic Arthritis; Subcutaneous Pediatric Dosage Regimen.

2.2 Recommended Dosage in Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dosage is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dosage is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Subcutaneous Pediatric Dosage Regimen

Administer Ustekinumab subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of Ustekinumab for pediatric patients 6 years of age and older with psoriatic arthritis, based on body weight, is shown below (Table 3).

Table 3: Recommended Dose of Ustekinumab for Subcutaneous Injection in Pediatric Patients 6 Years of Age and Older With Psoriatic Arthritis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg*	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

* For pediatric patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the vial.

2.3 Recommended Adult Dosage in Crohn's Disease

Intravenous Induction Adult Dosage Regimen

The recommended induction dosage is a single intravenous infusion using the weight-based dosage regimen specified in Table 4 *[see Dosage and Administration (2.7)]*.

Table 4: Initial Intravenous Dose of Ustekinumab in Adult Patients with Crohn's Disease

Body Weight of Patient at the Time of Dosing	Dose
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.4 Recommended Pediatric Dosage in Crohn's Disease

Intravenous Induction Pediatric Dosage Regimen

The recommended induction dosage in pediatric patients weighing 10 kg and above is a single intravenous infusion using the weight-based dosage regimen specified in Table 5 *[see Dosage and Administration (2.7)]*.

Table 5: Initial Intravenous Dose of Ustekinumab in Pediatric Patients (Weighing 10 kg or More) with Crohn's Disease

Body Weight of Patient at the Time of Dosing	Dose
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Subcutaneous Maintenance Pediatric Dosage Regimen

The recommended maintenance dosage in pediatric patients using weight-based dosing is:

- *10 kg to 35 kg*: a subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *greater than 35 kg*: a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.5 Recommended Dosage in Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

The recommended induction dosage is a single intravenous infusion using the weight-based dosage regimen specified in Table 6 *[see Dosage and Administration (2.7)]*.

Table 6: Initial Intravenous Dosage of Ustekinumab in Adult Patients with Ulcerative Colitis

Body Weight of Patient at the Time of Dosing	Dose
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.6 General Considerations for Administration

- Ustekinumab is intended for use under the guidance and supervision of a healthcare provider. Ustekinumab should only be administered to patients who will be closely monitored and have regular follow-up visits with a healthcare provider. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In pediatric patients, it is recommended that Ustekinumab be administered by a healthcare provider. If a healthcare provider determines that it is appropriate, a patient may self-inject or a caregiver may inject Ustekinumab after proper training in subcutaneous injection technique. Instruct patients to follow the directions provided in the Instructions for Use *[see Instructions for Use]*.

- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.

- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.

- Prior to administration, visually inspect Ustekinumab for particulate matter and discoloration. Ustekinumab is a colorless to light yellow solution and may contain a few small translucent or white particles. Do not use Ustekinumab if it is discolored or cloudy, or if other particulate matter is present. Ustekinumab does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

2.7 Preparation and Administration of Ustekinumab 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease and Ulcerative Colitis)

Ustekinumab solution for intravenous infusion must be diluted, prepared, and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of vials needed based on patient weight (see Table 4, Table 5, and Table 6 above).

2. Obtain the appropriate infusion solution (Table 7). Withdraw and discard a volume of the infusion solution equal to the volume of Ustekinumab solution to be added:

Table 7: Appropriate Infusion Solution and Final Infusion Volumes for Intravenous Infusion of Ustekinumab Solution

Patient Population	Body Weight of Patient at the Time of Dosing	Infusion Solution	Final Volume in the Infusion Bag
Pediatric	10 kg to 25 kg	0.9% Sodium Chloride Injection	100 mL[a]
	Greater than 25 kg	0.9% Sodium Chloride Injection	250 mL[a]
Adult	All weights	0.45% or 0.9% Sodium Chloride Injection	250 mL[a]

[a] Remove a volume of infusion solution equal to the volume of Ustekinumab solution to be added to obtain the final volume.

3. Add the volume of Ustekinumab solution equal to the calculated dose of Ustekinumab to the infusion solution and gently mix.

4. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discoloration or foreign particles are observed.

5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completely administered within the storage time *(see Storage below)*.

6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).

7. Do not infuse Ustekinumab concomitantly in the same intravenous line with other agents.

8. Ustekinumab does not contain preservatives. Each vial is for a one-time use in only one patient. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

9. Discard any unused portion of the infusion solution.

Storage

Do not freeze.

Storage time at room temperature begins once the diluted solution has been prepared.

100 mL infusion bag:

- If necessary, the diluted infusion solution may be kept at room temperature up to 25 °C (77 °F) for **up to 3 hours.**
- The infusion should be completed **within 4 hours** after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period).

250 mL infusion bag:

- If necessary, the diluted infusion solution may be kept at room temperature up to 25 °C (77 °F) for up to 7 hours.
- The infusion should be completed within 8 hours after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period).

3 DOSAGE FORMS AND STRENGTHS

Ustekinumab is a colorless to light yellow solution and may contain a few small translucent or white particles.

Subcutaneous Injection

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe
- Injection: 45 mg/0.5 mL solution in a single-dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

Ustekinumab is contraindicated in patients with clinically significant hypersensitivity to any ustekinumab product or to any of the excipients in Ustekinumab *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Ustekinumab may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving Ustekinumab *[see Adverse Reactions (6.1, 6.3)]*.

Serious infections requiring hospitalization, or otherwise clinically significant infections, reported in clinical trials included the following:

- *Plaque Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis, and urinary tract infections.
- *Psoriatic arthritis*: cholecystitis.
- *Crohn's disease in adults*: anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis.
- *Crohn's disease in pediatrics*: Aeromonas gastroenteritis
- *Ulcerative colitis*: gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Avoid initiating treatment with Ustekinumab in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of Ustekinumab in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with Ustekinumab and discontinue Ustekinumab for serious or clinically significant infections until the infection resolves or is adequately treated.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with Ustekinumab may be susceptible to these types of infections. Consider appropriate diagnostic testing, (e.g., tissue culture, stool culture, as dictated by clinical circumstances).

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with Ustekinumab.

Avoid administering Ustekinumab to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering Ustekinumab. Consider anti-tuberculosis therapy prior to initiation of Ustekinumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving Ustekinumab for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

Ustekinumab is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received Ustekinumab in clinical trials *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13.1)]*.

The safety of Ustekinumab has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving Ustekinumab who had pre-existing risk factors for developing non-melanoma skin cancer. Monitor all patients receiving Ustekinumab for the appearance of non-melanoma skin cancer. Closely follow patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment *[see Adverse Reactions (6.1)]*.

5.5 Serious Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with Ustekinumab in clinical trials and postmarketing. Some serious hypersensitivity reactions have occurred during the first intravenous dose of Ustekinumab *[see Adverse Reactions (6.1, 6.3)]*.

If a severe or clinically significant hypersensitivity reaction occurs, discontinue Ustekinumab immediately and initiate appropriate medical treatment *[see Contraindications (4)]*.

5.6 Posterior Reversible Encephalopathy Syndrome (PRES)

Two cases of posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis, psoriatic arthritis, and Crohn's disease. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab.

Monitor all patients treated with Ustekinumab for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment and discontinue Ustekinumab.

5.7 Immunizations

Prior to initiating therapy with Ustekinumab, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with Ustekinumab should avoid receiving live vaccines. Avoid administering BCG vaccines during treatment with Ustekinumab or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving Ustekinumab because of the potential risk for shedding from the household contact and transmission to patient.

Non-live vaccinations received during a course of Ustekinumab may not elicit an immune response sufficient to prevent disease.

5.8 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of Ustekinumab. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue Ustekinumab and institute appropriate treatment *[see Adverse Reactions (6.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.4)]*
- Serious Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.6)]*
- Noninfectious Pneumonia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to Ustekinumab in 3117 adult subjects with plaque psoriasis, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed

for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 8 summarizes the adverse reactions that occurred at a rate of at least 1% with higher rates in the Ustekinumab groups during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 8: Adverse Reactions, Reported by ≥1% of Subjects with Plaque Psoriasis and at Higher Rates in the Ustekinumab groups through Week 12 in Ps STUDY 1 and Ps STUDY 2

		Ustekinumab	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

Adverse reactions that occurred at rates less than 1% in the controlled period of Ps STUDIES 1 and 2 through week 12 included: cellulitis, herpes zoster, diverticulitis, and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

One case of PRES occurred during clinical trials in adult subjects with plaque psoriasis *[see Warnings and Precautions (5.6)]*.

Infections

In the placebo-controlled period of clinical trials of subjects with plaque psoriasis (average follow-up of 12.6 weeks for subjects receiving placebo and 13.4 weeks for Ustekinumab-treated subjects), 27% of Ustekinumab-treated subjects reported infections (1.39 per patient-years of follow-up) compared with 24% of subjects receiving placebo (1.21 per patient-years of follow-up). Serious infections occurred in 0.3% of Ustekinumab-treated subjects (0.01 per patient-years of follow-up) and in 0.4% of subjects receiving placebo (0.02 per patient-years of follow-up) *[see Warnings and Precautions (5.1)]*.

In the controlled and non-controlled portions of clinical trials in subjects with plaque psoriasis (median follow-up of 3.2 years), representing 8998 patient-years of exposure, 72.3% of Ustekinumab-treated subjects reported infections (0.87 per patient-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per patient-years of follow-up).

Malignancies

In the controlled and non-controlled portions of clinical trials in subjects with plaque psoriasis (median follow-up of 3.2 years, representing 8998 patient-years of exposure), 1.7% of Ustekinumab-treated subjects reported malignancies excluding non-melanoma skin cancers

(0.60 per hundred patient-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of Ustekinumab-treated subjects (0.52 per hundred patient-years of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical trials were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in Ustekinumab-treated subjects during the controlled and uncontrolled portions of trials were similar in type and number to what would be expected in the general U.S. population according to the 1969-2004 SEER database (adjusted for age, gender and race).

Pediatric Subjects with Plaque Psoriasis

The safety of Ustekinumab was assessed in two trials of pediatric subjects with moderate to severe plaque psoriasis. Ps STUDY 3 evaluated safety for up to 60 weeks in 110 pediatric subjects 12 to 17 years old. Ps STUDY 4 evaluated safety for up to 56 weeks in 44 pediatric subjects 6 to 11 years old. The safety profile in pediatric subjects was similar to the safety profile from trials in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of Ustekinumab was assessed in 927 subjects in two randomized, double-blind, placebo-controlled trials in adults with active psoriatic arthritis (PsA). The overall safety profile of Ustekinumab in subjects with PsA was consistent with the safety profile seen in clinical trials in adult subjects with plaque psoriasis. A higher incidence of arthralgia, nausea, and dental infections was observed in Ustekinumab-treated subjects when compared with placebo-treated subjects (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical trials.

Adult Subjects with Crohn's Disease

The safety of Ustekinumab was assessed in 1407 subjects with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials. These 1407 subjects included 40 subjects who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In trials CD-1 and CD-2 there were 470 subjects who received Ustekinumab 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Subjects who were responders in either trial CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg Ustekinumab every 8 weeks, or placebo for 44 weeks in trial CD-3. Subjects in these 3 trials may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of Ustekinumab was consistent with the safety profile seen in the clinical trials in adult subjects with plaque psoriasis and psoriatic arthritis. Common adverse reactions in trials CD-1 and CD-2 and in trial CD-3 are listed in Tables 9 and 10, respectively.

Table 9: Common Adverse Reactions Through Week 8 in Trials CD-1 and CD-2 occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Subjects Receiving Placebo

	Placebo N=466	Ustekinumab 6 mg/kg Single Intravenous Induction Dose N=470
Vomiting	3%	4%

Other less common adverse reactions reported in subjects in trials CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 10: Common Adverse Reactions Through Week 44 in Trial CD-3 occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Subjects Receiving Placebo

	Placebo N=133	Ustekinumab 90 mg Subcutaneous Maintenance Dose Every 8 Weeks N=131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In subjects with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes zoster were reported in one subject each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical trials, 0.2% of Ustekinumab-treated subjects (0.36 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of Ustekinumab-treated subjects (0.27 events per hundred patient-years) and in none of the placebo-treated subjects.

Hypersensitivity Reactions Including Anaphylaxis

In CD trials, two subjects reported hypersensitivity reactions following Ustekinumab administration. One subject experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of subjects receiving subcutaneous Ustekinumab). In addition, one subject experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous Ustekinumab dose (0.08% of subjects receiving intravenous Ustekinumab). These subjects were

treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour *[see Warnings and Precautions (5.5)]*.

Pediatric Subjects 2 Years of Age and Older with Crohn's Disease

The safety of Ustekinumab has been studied in 101 pediatric subjects (2 to 17 years of age) with moderately to severely active Crohn's disease and 48 subjects received the recommended maintenance dosage *[see Clinical Studies (14.5)]*. In general, adverse reactions reported in the clinical trial of pediatric subjects with Crohn's disease were similar to those reported in adult subjects with Crohn's disease in Studies CD-1, CD-2, and CD-3 *[see Clinical Studies (14.4)]*. Other adverse reactions reported in at least 10% of pediatric subjects were upper respiratory tract infection (13% during induction and 17% during maintenance), COVID-19 (17% during maintenance), and headache (10% during maintenance).

One pediatric subject discontinued treatment with Ustekinumab after developing anaphylactic shock within the first two minutes of initiation of the first intravenous infusion and was stabilized with medical intervention *[see Warnings and Precautions (5.5)]*.

Ulcerative Colitis

The safety of Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical trials (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult subjects with moderately to severely active ulcerative colitis *[see Clinical Studies (14.6)]*. The overall safety profile of Ustekinumab in subjects with ulcerative colitis was consistent with the safety profile seen across all approved indications. Adverse reactions reported in at least 3% of Ustekinumab-treated subjects and at a higher rate than placebo were:

- Induction (UC-1): nasopharyngitis (7% vs 4%).
- Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs. 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

Infections

In subjects with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one subject each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the ulcerative colitis clinical trials, 0.4% of Ustekinumab-treated subjects (0.48 events per hundred patient-years) and 0.0% of subjects receiving placebo (0.00 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.5% of Ustekinumab-treated subjects (0.64 events per hundred patient-years) and 0.2% of subjects receiving placebo (0.40 events per hundred patient-years).

6.2 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in studies of other ustekinumab products. Approximately 6 to 12.4% of subjects treated with Ustekinumab in clinical trials in subjects with plaque psoriasis and psoriatic arthritis developed antibodies to ustekinumab, which were generally low-titer. In clinical trials in subjects with plaque psoriasis, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In trials in subjects with plaque psoriasis, the majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies.

In clinical trials in subjects with Crohn's disease and ulcerative colitis, 2.9% and 4.6% of subjects, respectively, developed antibodies to ustekinumab when treated with Ustekinumab for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of Ustekinumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Ustekinumab exposure.

Immune system disorders: Hypersensitivity reactions (e.g., anaphylaxis, angioedema, dyspnea, rash, urticaria), including a fatal case that presented with chest tightness and dyspnea during infusion of the first dose.

Infections and infestations: Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis).

Neurological disorders: Posterior Reversible Encephalopathy Syndrome (PRES).

Respiratory, thoracic, and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis, hypersensitivity vasculitis.

7 DRUG INTERACTIONS

7.1 Concomitant Therapies

In trials in subjects with plaque psoriasis the safety of Ustekinumab in combination with immunosuppressive agents or phototherapy has not been evaluated. In trials in subjects with psoriatic arthritis, concomitant MTX use did not appear to influence the safety or efficacy of Ustekinumab. In trials in subjects with Crohn's disease (CD-1 and CD-2) and ulcerative colitis (UC-1), immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of subjects and corticosteroids were used concomitantly in approximately 40% and 50% of

Crohn's disease and ulcerative colitis subjects, respectively. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of Ustekinumab.

7.2 CYP450 Substrates

The formation of CYP450 enzymes can be suppressed by increased levels of certain cytokines (e.g., IL-1, IL-6, TNFα, IFN) during chronic inflammation. Thus, use of Ustekinumab, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation or discontinuation of Ustekinumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and adjust the individual dosage of the CYP substrate as needed. See the prescribing information of specific CYP substrates.

A CYP-mediated drug interaction effect was not observed in subjects with Crohn's disease *[see Clinical Pharmacology (12.3)]*.

7.3 Allergen Immunotherapy

Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab may decrease the protective effect of allergen immunotherapy (decrease tolerance) which may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Ustekinumab Pregnancy Registry, published literature and pharmacovigilance in pregnant women have not identified a Ustekinumab-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother and the fetus associated with inflammatory bowel disease (IBD) in pregnancy. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed in offspring after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the maximum recommended human dose (MRHD).
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with IBD is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Therefore, Ustekinumab may be present in infants exposed *in utero*. The potential clinical impact of ustekinumab exposure in infants exposed *in utero* should be considered.

Data

Human Data

An observational pregnancy registry conducted by (OTIS)/MotherToBaby in the U.S. and Canada (enrollment between 2013 and 2019) assessed the risk of major birth defects, pattern of major and minor anomalies in live-born infants, miscarriage, and adverse infant outcomes in women with Ustekinumab exposure. In the registry study, there were 101 participants and 107 pregnancies with exposure to Ustekinumab (88 prospective; 19 retrospective). Most participants had a primary indication of CD (65.4%) or psoriasis (30.8%). The pregnancy registry did not identify a Ustekinumab-associated risk of major birth defects, pattern of major or minor anomalies, increased risk of miscarriage or adverse infant outcomes. Methodological limitations of the registry include small sample size, lack of an internal comparison group, a mix of prospective and retrospective reports, and unmeasured confounders. The conclusions from the pregnancy registry were consistent with the published literature and pharmacovigilance.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the MRHD from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related-effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

Limited data from published literature suggests that ustekinumab is present in human breast milk. There are no available data on the effects of ustekinumab on milk production. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ustekinumab are unknown. No adverse effects on the breastfed infant causally related to ustekinumab have been identified in the published literature or postmarketing experience.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ustekinumab and any potential adverse effects on the breastfed child from Ustekinumab or from the underlying maternal condition.

8.4 Pediatric Use

Plaque Psoriasis

The safety and effectiveness of Ustekinumab have been established for the treatment of moderate to severe plaque psoriasis in pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy.

Use of Ustekinumab in pediatric patients 12 to less than 17 years of age is supported by evidence from a multicenter, randomized, 60 week trial (Ps STUDY 3) that included a 12 week, double-blind, placebo-controlled, parallel group portion, in 110 pediatric subjects 12 years of age and older *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

Use of Ustekinumab in pediatric patients 6 to 11 years of age is supported by evidence from an open-label, single-arm, efficacy, safety, and pharmacokinetics trial (Ps STUDY 4) in 44 subjects *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

The safety and effectiveness of Ustekinumab have not been established in pediatric patients less than 6 years of age with plaque psoriasis.

Psoriatic Arthritis

The safety and effectiveness of Ustekinumab have been established for treatment of psoriatic arthritis in pediatric patients 6 years of age and older.

Use of Ustekinumab in these age groups is supported by evidence from adequate and well controlled trials of Ustekinumab in adult subjects with psoriasis and PsA, pharmacokinetic data from adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and safety data from two clinical trials in 44 pediatric subjects 6 to 11 years old with psoriasis and 110 pediatric subjects 12 years of age and older with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric subjects with PsA *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1, 14.2, 14.3)]*.

The safety and effectiveness of Ustekinumab have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

Crohn's Disease

The safety and effectiveness of Ustekinumab for the treatment of moderately to severely active Crohn's disease have been established in pediatric patients aged 2 years and older. Use of Ustekinumab for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety, efficacy, and pharmacokinetic data from a 52-week study in 101 pediatric subjects aged 2 to 17 years of age. The adverse reaction profile in these pediatric subjects was similar to adverse reactions reported in the clinical trials of adults with Crohn's

disease. Other adverse reactions reported in at least 10% of pediatric subjects were upper respiratory tract infection (13% during induction and 17% during maintenance), COVID-19 (17% during maintenance), and headache (10% during maintenance). Serum concentrations in pediatric subjects with Crohn's disease, were generally comparable to those in the adult Crohn's disease population. *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4, 14.5)]*.

The safety and effectiveness of Ustekinumab for the treatment of moderately to severely active Crohn's disease have not been established in pediatric patients less than 2 years of age.

Ulcerative Colitis

The safety and effectiveness of Ustekinumab have not been established in pediatric patients with ulcerative colitis.

8.5 Geriatric Use

Of the 6709 subjects exposed to Ustekinumab, a total of 340 were 65 years of age or older (183 subjects with plaque psoriasis, 65 subjects with psoriatic arthritis, 58 subjects with Crohn's disease, and 34 subjects with ulcerative colitis), and 40 subjects were 75 years of age or older. Clinical trials of Ustekinumab did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

11 DESCRIPTION

Ustekinumab, a human IgG1κ monoclonal antibody, is a human interleukin-12 and -23 antagonist. Using DNA recombinant technology, ustekinumab is produced in a murine cell line (Sp2/0). The manufacturing process contains steps for the clearance of viruses. Ustekinumab is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

Ustekinumab injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles with pH of 5.7-6.3.

Ustekinumab for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab in 0.5 mL in a single-dose Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cover that contains dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

Ustekinumab for Intravenous Infusion

Available as 130 mg of ustekinumab in 26 mL, supplied as a single-dose Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg), and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a human IgG1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12Rβ1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease and ulcerative colitis. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

12.2 Pharmacodynamics

Plaque Psoriasis

In a small exploratory trial, a decrease was observed in the expression of mRNA of its molecular targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-treatment in subjects with plaque psoriasis.

Ulcerative Colitis

In both trial UC-1 (induction) and trial UC-2 (maintenance), a positive relationship was observed between exposure and rates of clinical remission, clinical response, and endoscopic improvement. The response rate approached a plateau at the ustekinumab exposures associated with the recommended dosing regimen for maintenance treatment *[see Clinical Studies (14.6)]*.

12.3 Pharmacokinetics

Absorption

In adult subjects with plaque psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with plaque psoriasis.

Following multiple subcutaneous doses of Ustekinumab in adult subjects with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for subjects less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for subjects greater than 100 kg receiving a 90 mg dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL in subjects with Crohn's disease, and 129.1 ± 27.6 mcg/mL in subjects with ulcerative colitis. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean ±SD steady-state trough concentration was 2.5 ± 2.1 mcg/mL in subjects with Crohn's disease, and 3.3 ± 2.3 mcg/mL in subjects with ulcerative colitis for 90 mg ustekinumab administered every 8 weeks.

Distribution

Population pharmacokinetic analyses showed that the volume of distribution of ustekinumab in the central compartment was 2.7 L (95% CI: 2.69, 2.78) in subjects with Crohn's disease and 3.0 L (95% CI: 2.96, 3.07) in subjects with ulcerative colitis. The total volume of distribution at steady-state was 4.6 L in subjects with Crohn's disease and 4.4 L in subjects with ulcerative colitis.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all trials in subjects with plaque psoriasis following subcutaneous administration. Population pharmacokinetic analyses showed that the clearance of ustekinumab was 0.19 L/day (95% CI: 0.185, 0.197) in subjects with Crohn's disease and 0.19 L/day (95% CI: 0.179, 0.192) in subjects with ulcerative colitis with an estimated median terminal half-life of approximately 19 days for both IBD (Crohn's disease and ulcerative colitis) populations.

These results indicate the pharmacokinetics of ustekinumab were similar between subjects with Crohn's disease and ulcerative colitis.

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody, ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

Weight

When given the same dose, subjects with plaque psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of

higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 subjects with plaque psoriasis greater than or equal to 65 years old) was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects older than 65 years old.

Age: Pediatric Population

Following multiple recommended doses of Ustekinumab in pediatric subjects 6 years of age and older with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL and 0.54 ± 0.43 mcg/mL, respectively, in pediatric subjects 6 to 11 years of age and pediatric subjects 12 years of age and older.

Overall, the observed steady-state ustekinumab trough concentrations in pediatric subjects with plaque psoriasis were within the range of those observed for adult subjects with plaque psoriasis and adult subjects with PsA after administration of Ustekinumab.

The pharmacokinetics of ustekinumab were studied in pediatric subjects with Crohn's disease aged 2 to 17 years and weighing 13 to 88 kg. There are no clinically significant differences in serum ustekinumab exposure expected between adult patients and pediatric patients with Crohn's disease who receive the recommended dosage *[see Dosage and Administration (2.4)]*.

Drug Interaction Studies

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosage in subjects with Crohn's disease *[see Drug Interactions (7.2)]*.

Population pharmacokinetic analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in subjects with psoriatic arthritis.

In subjects with Crohn's disease and ulcerative colitis, population pharmacokinetic analyses did not indicate changes in ustekinumab clearance with concomitant use of corticosteroids or immunomodulators (AZA, 6-MP, or MTX); and serum ustekinumab concentrations were not impacted by concomitant use of these medications.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of Ustekinumab. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

14.1 Adult Subjects with Plaque Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled trials (Ps STUDY 1 and Ps STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the trials.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The trials had the same design through Week 28. In both trials, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of Ustekinumab. Subjects randomized to Ustekinumab received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive Ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16.

In both trials, subjects in all treatment groups had a median baseline PASI score ranging from approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in Ps STUDY 1 and 40% of subjects in Ps STUDY 2. Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. A total of 28% of subjects had a history of psoriatic arthritis.

In both trials, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 11 below.

Table 11: Clinical Outcomes at Week 12 in Adult Subjects with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		Ustekinumab			Ustekinumab	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

Examination of age, gender, and race subgroups did not identify differences in response to Ustekinumab among these subgroups.

In subjects who weighed 100 kg or less, response rates were comparable with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 12 below).

Table 12: Clinical Outcomes by Weight at Week 12 in Adult Subjects with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
		Ustekinumab			Ustekinumab	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Subjects randomized	**255**	**255**	**256**	**410**	**409**	**411**
PASI 75 response*						
≤100 kg	4%	74%	65%	4%	73%	78%
	6/166	124/168	107/164	12/290	218/297	225/289
>100 kg	2%	54%	68%	3%	49%	71%
	2/89	47/87	63/92	3/120	55/112	86/121
PGA of Cleared or Minimal*						
≤100 kg	4%	64%	63%	5%	74%	75%
	7/166	108/168	103/164	14/290	220/297	216/289
>100 kg	3%	49%	58%	3%	51%	69%
	3/89	43/87	53/92	4/120	57/112	84/121

* Subjects were dosed with trial medication at Weeks 0 and 4.

Subjects in Ps STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at Week 40 to either continued dosing of Ustekinumab (Ustekinumab at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to Ustekinumab treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Pediatric Subjects with Plaque Psoriasis

A multicenter, randomized, double blind, placebo-controlled trial (Ps STUDY 3) enrolled 110 pediatric subjects 12 years of age and older with a minimum BSA involvement of 10%, a PASI score greater than or equal to 12, and a PGA score greater than or equal to 3, who were candidates for phototherapy or systemic therapy and whose disease was inadequately controlled by topical therapy.

Subjects were randomized to receive placebo (n = 37), the recommended dose of Ustekinumab (n = 36), or one-half the recommended dose of Ustekinumab (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of Ustekinumab was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing 60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive Ustekinumab at the recommended dose or one-half the recommended dose.

Of the pediatric subjects, approximately 63% had prior exposure to phototherapy or conventional systemic therapy and approximately 11% had prior exposure to biologics.

The endpoints were the proportion of subjects who achieved a PGA score of cleared (0) or minimal (1), PASI 75, and PASI 90 at Week 12. Subjects were followed for up to 60 weeks following first administration of trial agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 13.

Table 13: Efficacy Results at Week 12 in Pediatric Subjects 12 Years of Age and Older with Plaque Psoriasis in Ps STUDY 3

	Ps STUDY 3	
	Placebo n (%)	**Ustekinumab* n (%)**
N	**37**	**36**
PGA		
PGA of Cleared (0) or Minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1 and Table 2.

14.3 Psoriatic Arthritis

The safety and efficacy of Ustekinumab was assessed in 927 subjects (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled trials in adult subjects 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite nonsteroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Subjects in these trials had a diagnosis of PsA for at least 6 months. Subjects with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal

interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Subjects were randomized to receive treatment with Ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of subjects continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of subjects achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the subjects, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)-α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the subjects had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both trials, a greater proportion of subjects achieved ACR 20, ACR 50 and PASI 75 response in the Ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 14). ACR 70 responses were also higher in the Ustekinumab 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were consistent in subjects treated with Ustekinumab alone or in combination with methotrexate. Responses were similar in subjects regardless of prior TNFα exposure.

Table 14: ACR 20, ACR 50, ACR 70 and PASI 75 Responses In PsA STUDY 1 And PsA STUDY 2 At Week 24

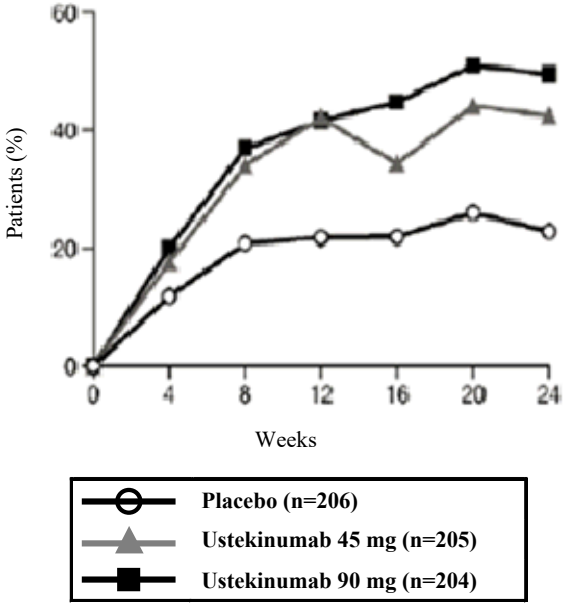
	PsA STUDY 1			**PsA STUDY 2**		
		Ustekinumab			**Ustekinumab**	
	Placebo	**45 mg**	**90 mg**	**Placebo**	**45 mg**	**90 mg**
Number of subjects randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of subjects with ≥ 3% BSA[a]	**146**	**145**	**149**	**80**	**80**	**81**
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

[a] Number of subjects with ≥ 3% BSA psoriasis skin involvement at baseline

The percent of subjects achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of subjects achieving ACR 20 response through Week 24

PsA STUDY 1



The results of the components of the ACR response criteria are shown in Table 15.

Table 15: Mean Change From Baseline In ACR Components At Week 24

	PsA STUDY 1		
		Ustekinumab	
	Placebo (N = 206)	**45 mg (N = 205)**	**90 mg (N = 204)**
Number of swollen joints[a]			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints[b]			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Subject's assessment of pain[c]			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Subject global assessment[c]			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment[c]			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)[d]			
Baseline	1.2	1.2	1.2

Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)[e]			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

[a] Number of swollen joints counted (0-66)

[b] Number of tender joints counted (0-68)

[c] Visual analog scale; 0= best, 10=worst.

[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e] CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each Ustekinumab group compared with placebo at Week 24.

Physical Function

Ustekinumab-treated subjects showed improvement in physical function compared to subjects receiving placebo as assessed by HAQ-DI at Week 24. In both trials, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the Ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24.

14.4 Adult Crohn's Disease

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult subjects with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction trials (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance trial (CD-3) representing 52 weeks of therapy. Subjects in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while subjects in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Trials CD-1 and CD-2

In trials CD-1 and CD-2, 1409 subjects were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both trials, subjects were randomized to receive a single intravenous administration of Ustekinumab at either approximately 6 mg/kg, placebo (see Table 4), or 130 mg (a lower dose than recommended).

In trial CD-1, subjects had failed or were intolerant to prior treatment with a TNF blocker: 29% subjects had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these subjects, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the trial, approximately 46% of the subjects were receiving corticosteroids and 31% of the subjects were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 319 in the Ustekinumab approximately 6 mg/kg group and 313 in the placebo group.

In trial CD-2, subjects had failed or were intolerant to prior treatment with corticosteroids (81% of subjects), at least one immunomodulator (6-MP, AZA, MTX; 68% of subjects), or both (49% of subjects). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the trial, approximately 39% of the subjects were receiving corticosteroids and 35% of the subjects were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the Ustekinumab and 290 in the placebo group.

In these induction trials, a greater proportion of subjects treated with Ustekinumab (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 16 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in Ustekinumab-treated subjects and continued to improve through Week 8.

Table 16: Induction of Clinical Response and Remission in CD-1[*] and CD-2[**]

	CD-1 n = 741			CD-2 n = 627		
	Placebo N = 247	Ustekinumab [†] N = 249	Treatment Difference and 95% CI	Placebo N = 209	Ustekinumab [†] N = 209	Treatment Difference and 95% CI
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[a]	12% (4%, 20%)	60 (29%)	116 (56%)[b]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[b]	14% (8%, 20%)	41 (20%)	84 (40%)[b]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[b]	18% (10%, 25%)	67 (32%)	121 (58%)[b]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[a]	13% (5%, 22%)	81 (39%)	135 (65%)[b]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[a]	13% (5%, 22%)	66 (32%)	106 (51%)[b]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

[*] Patient population consisted of subjects who failed or were intolerant to TNF blocker therapy

[**] Patient population consisted of subjects who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-MP, AZA, MTX) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.

[†] Infusion dose of Ustekinumab using the weight-based dosage regimen specified in Table 4.

[a] $0.001 \leq p < 0.01$

[b] $p < 0.001$

Trial CD-3

The maintenance trial (CD-3), evaluated 388 subjects who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with either induction dose of Ustekinumab in trials CD-1 or CD-2. Subjects were randomized to receive a subcutaneous maintenance regimen of either 90 mg Ustekinumab every 8 weeks or placebo for 44 weeks (see Table 17).

Table 17: Clinical Response and Remission In CD-3 (Week 44; 52 Weeks From Initiation Of Induction Dose)

	Placebo[*] N = 131[†]	90 mg Ustekinumab Every 8 Weeks N = 128[†]	Treatment Difference and 95% CI
Clinical Remission	47 (36%)	68 (53%)[a]	17% (5%, 29%)

Clinical Response	58 (44%)	76 (59%)[b]	15% (3%, 27%)
Clinical Remission in Patients in Remission at the Start of Maintenance Therapy[**]	36/79 (46%)	52/78 (67%)[a]	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

[*] The placebo group consisted of subjects who were in response to Ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

[**] Subjects in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

[†] Subjects who achieved clinical response to Ustekinumab at the end of the induction trial.

[a] $p < 0.01$

[b] $0.01 \leq p < 0.05$

At Week 44, 47% of subjects who received Ustekinumab were corticosteroid-free and in clinical remission, compared to 30% of subjects in the placebo group.

At Week 0 of trial CD-3, 34/56 (61%) Ustekinumab-treated subjects who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these subjects were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) subjects were in clinical remission at Week 0 while 16/61 (26%) of these subjects were in remission at Week 44.

At Week 0 of trial CD-3, 46/72 (64%) Ustekinumab-treated subjects who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these subjects were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these subjects were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these subjects who were also naïve to TNF blockers, 34/52 (65%) of Ustekinumab-treated subjects were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Subjects who were not in clinical response 8 weeks after Ustekinumab induction were not included in the primary efficacy analyses for trial CD-3; however, these subjects were eligible to receive a 90 mg subcutaneous injection of Ustekinumab upon entry into trial CD-3. Of these subjects, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the trial.

14.5 Pediatric Crohn's Disease

The efficacy and safety of Ustekinumab was evaluated in 101 pediatric patients aged 2 years to 17 years in a multi-center trial consisting of an open-label intravenous 8-week induction phase followed by randomization to one of two subcutaneous dosage regimens in a 44-week double-blind maintenance phase representing 52 weeks of therapy. Efficacy analyses were conducted in 93 patients with moderately to severely active Crohn's disease (NCT04673357).

Pediatric patients enrolled in the study had an inadequate response or were intolerant to treatment with oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) and/or prior biologic therapy, (TNF blockers or vedolizumab).

Of the 93 subjects included in the efficacy analyses, the mean age was 14 years (range 5 to 17 years), the median weight was 49 kg, and 39% were female. Additionally, 99% identified as not Hispanic or Latino and 1% as not reported; 89% identified as White, 8% as Asian, 2% as Black

or African American, and 1% as not reported. The median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 and the median Simple Endoscopic Score for Crohn's Disease (SES-CD) was 12.

Patients received induction treatment with a single Ustekinumab intravenous dose, of approximately 6 mg/kg (patients weighing 40 kg or more) or 250 mg/m^2 (patients weighing less than 40 kg, based on body surface area [BSA]), followed by a randomized double-blind subcutaneous maintenance regimen of 90 mg Ustekinumab (patients weighing 40 kg or more) or 60 mg/m^2 Ustekinumab (patients weighing less than 40 kg, based on BSA) every 8 weeks or another subcutaneous dosage regimen.

The recommended dosage for pediatric patients weighing 10 kg to less than 40 kg differs from the BSA-based dosage in this study. There are no anticipated clinically relevant differences in efficacy between the recommended and studied pediatric dosages of Ustekinumab *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

The primary endpoint of the study was clinical remission at Week 52 (from initiation of induction) which was evaluated in the subset of patients who achieved clinical response at Week 8.

Efficacy Results

At Week 8, the proportion of patients who achieved clinical remission (defined as PCDAI score of ≤10) was 46% (43/93).

The proportion of patients in clinical response at Week 8, defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30, was 87% (81/93).

Of the 81 patients who received intravenous induction treatment and achieved clinical response or remission at Week 8, there were 39 patients who received the subcutaneous maintenance dosage described above every 8 weeks. Efficacy endpoints assessed at Week 52, including clinical response and/or remission (shown in Table 18), were assessed in this subset of patients.

Table 18: Proportion of Pediatric Patients 2 Years of Age and Older with Moderately to Severely Active Crohn's Disease Meeting Efficacy Endpoints at Week 52 (From Initiation of Induction) in a Clinical Trial

Endpoint	90 mg or 60 mg/m^2 Ustekinumab Every 8 Weeks[a] n/N (%) [95% CI]
Clinical Remission[b]	20/39 (51%) [36%, 66%]
Clinical Response[c]	23/39 (59%) [43%, 73%]
Clinical Remission in Patients in Clinical Remission at Week 8[d]	17/21 (81%) [59%, 93%]

[a] This subcutaneous dosage regimen followed 8 weeks after a single intravenous induction dose of approximately 6 mg/kg (patients weighing 40 kg or more) or 250 mg/m^2 (patients weighing less than 40 kg, based on body surface area [BSA]).

[b] Clinical remission is defined as PCDAI score ≤10.

[c] Clinical response is defined as reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30

[d] Endpoint was evaluated in subjects in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

At Week 52, the proportion of patients in endoscopic response, defined as a reduction in the SES-CD score of > 50% or SES-CD score ≤ 2, in patients with a baseline SES-CD score of ≥ 3, was 26% (10/39). The proportion of patients achieving corticosteroid-free clinical remission

defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week 52, was 49% (19/39).

14.6 Adult Ulcerative Colitis

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical trials [UC-1 and UC-2 (NCT02407236)] in adult subjects with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. The 8-week intravenous induction trial (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance trial (UC-2) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranged from 0 to 12 and has four subscores that were each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally-reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (Week 0) as Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥2. An endoscopy score of 2 was defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration. At baseline, subjects had a median Mayo score of 9, with 84% of subjects having moderate disease (Mayo score 6-10) and 15% having severe disease (Mayo score 11-12).

Subjects in these trials may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (AZA, 6-MP, or MTX), and oral corticosteroids (prednisone).

Trial UC-1

In UC-1, 961 subjects were randomized at Week 0 to a single intravenous administration of Ustekinumab of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Subjects enrolled in UC-1 had to have failed therapy with corticosteroids, immunomodulators or at least one biologic. A total of 51% had failed at least one biologic and 17% had failed both a TNF blocker and an integrin receptor blocker. Of the total population, 46% had failed corticosteroids or immunomodulators but were biologic-naïve and an additional 3% had previously received but had not failed a biologic. At induction baseline and throughout the trial, approximately 52% subjects were receiving oral corticosteroids, 28% subjects were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% subjects were receiving aminosalicylates.

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 19.

The secondary endpoints were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue

[neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue] are provided in Table 19.

In UC-1, a significantly greater proportion of subjects treated with Ustekinumab (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 19).

Table 19: Proportion of Subjects Meeting Efficacy Endpoints at Week 8 in UC-1

Endpoint	Placebo N = 319		Ustekinumab† N = 322		Treatment Difference and 97.5% CI [a]
	N	%	N	%	
Clinical Remission*	**22**	**7%**	**62**	**19%**	12% (7%, 18%) [b]
Bio-naïve‡	14/151	9%	36/147	24%	
Prior biologic failure	7/161	4%	24/166	14%	
Endoscopic Improvement§	**40**	**13%**	**80**	**25%**	12% (6%, 19%) [b]
Bio-naïve‡	28/151	19%	43/147	29%	
Prior biologic failure	11/161	7%	34/166	20%	
Clinical Response†	**99**	**31%**	**186**	**58%**	27% (18%, 35%) [b]
Bio-naïve‡	55/151	36%	94/147	64%	
Prior biologic failure	42/161	26%	86/166	52%	
Histologic-Endoscopic Mucosal Improvement‡	**26**	**8%**	**54**	**17%**	9% (3%, 14%) [b]
Bio-naïve‡	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

† Infusion dose of Ustekinumab using the weight-based dosage regimen specified in Table 4.

‡ An additional 7 subjects on placebo and 9 subjects on Ustekinumab (6 mg/kg) had been exposed to, but had not failed, biologics.

* Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

§ Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

† Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

‡ Histologic-endoscopic mucosal improvement was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1) and histologic improvement of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

[a] Adjusted treatment difference (97.5% CI)

[b] $p < 0.001$

The relationship of histologic-endoscopic mucosal improvement, as defined in UC-1, at Week 8 to disease progression and long-term outcomes was not evaluated during UC-1.

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in Ustekinumab-treated subjects.

Trial UC-2

The maintenance trial (UC-2) evaluated 523 subjects who achieved clinical response 8 weeks following the intravenous administration of either induction dose of Ustekinumab in UC-1. These subjects were randomized to receive a subcutaneous maintenance regimen of either 90 mg Ustekinumab every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks.

The primary endpoint was the proportion of subjects in clinical remission at Week 44. The secondary endpoints included the proportion of subjects maintaining clinical response at Week 44, the proportion of subjects with endoscopic improvement at Week 44, the proportion of subjects with corticosteroid-free clinical remission at Week 44, and the proportion of subjects maintaining clinical remission at Week 44 among subjects who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in subjects treated with Ustekinumab at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 20.

Table 20: Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	**Placebo* N = 175†**		**90 mg Ustekinumab Every 8 Weeks N = 176**		**Treatment Difference and 95% CI**
	N	**%**	**N**	**%**	
Clinical Remission**	**46**	**26%**	**79**	**45%**	19% (9%, 28%) [a]
Bio-naïve‡	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical Response at Week 44†	**84**	**48%**	**130**	**74%**	26% (16%, 36%) [a]
Bio-naïve‡	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement§	**47**	**27%**	**83**	**47%**	20% (11%, 30%) [a]
Bio-naïve‡	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remission‡	**45**	**26%**	**76**	**43%**	17% (8%, 27%) [a]
Bio-naïve‡	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in subjects who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%) [b]
Bio-naïve‡	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

‡ An additional 3 subjects on placebo and 6 subjects on Ustekinumab had been exposed to, but had not failed, biologics.

* The placebo group consisted of subjects who were in response to Ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

** Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

† Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

§ Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

‡ Corticosteroid-free clinical remission was defined as subjects in clinical remission and not receiving corticosteroids at Week 44.

a p=<0.001

b p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction

Subjects who were not in clinical response 8 weeks after induction with Ustekinumab in UC-1 were not included in the primary efficacy analyses for trial UC-2; however, these subjects were eligible to receive a 90 mg subcutaneous injection of Ustekinumab at Week 8. Of these subjects, 55/101 (54%) achieved clinical response eight weeks later (Week 16) and received Ustekinumab 90 mg subcutaneously every 8 weeks during the UC-2 trial. At Week 44, there were 97/157 (62%) subjects who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of subjects achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among subjects on Ustekinumab and 40/172 (23%) in subjects on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.

Endoscopic Normalization

Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At Week 8 in UC-1, endoscopic normalization was achieved in 25/322 (8%) of subjects treated with Ustekinumab and 12/319 (4%) of subjects in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of subjects treated with Ustekinumab and in 32/175 (18%) of subjects in placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ustekinumab injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes

- 45 mg/0.5 mL (NDC 57894-440-01)
- 90 mg/mL (NDC 57894-441-01)

Each prefilled syringe is equipped with a 27-gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

Single-dose Vial

- 45 mg/0.5 mL (NDC 57894-440-03)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 57894-444-01)

Storage and Stability

Store Ustekinumab vials and prefilled syringes refrigerated between 2 ºC to 8 ºC (36 ºF to 46 ºF). Store Ustekinumab vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

If needed, individual prefilled syringes may be stored at room temperature up to 30 °C (86 °F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, do not return to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use Ustekinumab after the expiration date on the carton or on the prefilled syringe.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that Ustekinumab may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients of the risk of developing malignancies while receiving Ustekinumab *[see Warnings and Precautions (5.4)]*.

Serious Hypersensitivity Reactions

- Inform patients that serious hypersensitivity reactions have been reported with intravenous and subcutaneous administration of Ustekinumab. Instruct patients to discontinue Ustekinumab and seek immediate medical attention if they experience any signs or symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.5)]*.

- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.6)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

Inform patients to immediately contact their healthcare provider if they experience signs and symptoms of PRES (which may include headache, seizures, confusion, or visual disturbances) *[see Warnings and Precautions (5.6)]*.

Immunizations

Inform patients that Ustekinumab can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions (5.7)]*.

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864 at Cilag AG, Schaffhausen, Switzerland

MEDICATION GUIDE
Ustekinumab (yü-stə-kin-ü-mab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about Ustekinumab?

Ustekinumab is a medicine that affects your immune system. Ustekinumab can increase your risk of having serious side effects, including:

- **Serious infections.** Ustekinumab may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections during treatment with Ustekinumab, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.
  - Your healthcare provider should check you for TB before starting Ustekinumab.
  - If your healthcare provider feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with Ustekinumab and during treatment with Ustekinumab.
  - Your healthcare provider should watch you closely for signs and symptoms of TB while you are being treated with Ustekinumab.

You should not start Ustekinumab if you have any kind of infection unless your healthcare provider says it is okay.

Before starting Ustekinumab, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection or have any open cuts.
- get a lot of infections or have infections that keep coming back.
- have TB or have been in close contact with someone with TB.

  After starting Ustekinumab, call your healthcare provider right away if you have any symptoms of an infection (see above). These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. Ustekinumab can make you more likely to get infections or make an infection that you have worse.

- **People who have** a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take Ustekinumab may also be more likely to get these infections.
- **Cancers.** Ustekinumab may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your healthcare provider if you have ever had any type of cancer. Some people who are receiving Ustekinumab and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with Ustekinumab, tell your healthcare provider if you develop any new skin growths.

What is Ustekinumab?

Ustekinumab is a prescription medicine used to treat:

- adults and children 6 years of age and older with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- adults and children 6 years of age and older with active psoriatic arthritis.
- adults and children 2 years of age and older with moderately to severely active Crohn's disease.
- adults with moderately to severely active ulcerative colitis.

It is not known if Ustekinumab is safe and effective in children less than 2 years of age with Crohn's disease, in children less than 18 years of age with ulcerative colitis or in children less than 6 years of age with plaque psoriasis or psoriatic arthritis.

Who should not use Ustekinumab?

Do not use Ustekinumab if you are allergic to any ustekinumab product or any of the ingredients in Ustekinumab. See the end of this Medication Guide for a complete list of ingredients in Ustekinumab.

Before you use or receive Ustekinumab, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section "**What is the most important information I should know about Ustekinumab?**"
- ever had an allergic reaction to Ustekinumab. Ask your healthcare provider if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.
- have recently received or are scheduled to receive an immunization (vaccine). People who are being treated with Ustekinumab should avoid receiving live vaccines. Tell your healthcare provider if anyone in your house needs a live vaccine. The viruses used in some types of live vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should avoid receiving the BCG vaccine during the 1 year before receiving Ustekinumab or 1 year after you stop receiving Ustekinumab**.
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with Ustekinumab. Ustekinumab may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- are pregnant or plan to become pregnant. It is not known if Ustekinumab can harm your unborn baby. You and your healthcare provider should decide if you will receive Ustekinumab.
- are breastfeeding or plan to breastfeed. Ustekinumab can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive Ustekinumab.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Ustekinumab?

- Use Ustekinumab exactly as the healthcare provider tells you to. The healthcare provider will determine the right dose of Ustekinumab, the amount for each injection, and how often it should be given. Be sure to keep all scheduled follow-up appointments.
- **The needle cover on the Ustekinumab prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults and children 2 years of age and older with Crohn's disease will receive the first dose of Ustekinumab through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. Ustekinumab will then be received as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of Ustekinumab, as described below.
- Adults with ulcerative colitis will receive the first dose of Ustekinumab through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. Ustekinumab will then be received as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of Ustekinumab, as described below.
- Adults and children 6 years of age and older with plaque psoriasis or psoriatic arthritis will receive Ustekinumab as an injection under the skin as described below.
- **Injecting Ustekinumab under the skin**
  - Ustekinumab is intended for use under the guidance and supervision of a healthcare provider.
  - In children, it is recommended that Ustekinumab be administered by a healthcare provider. If a healthcare provider decides that you or a caregiver may give the injections of Ustekinumab at home, you or a caregiver should receive training on the right way to prepare and inject Ustekinumab.
  - Do not try to inject Ustekinumab until you have been shown how to inject Ustekinumab by a healthcare provider.
  - Ustekinumab can be injected under the skin in the upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).

- Do not give an injection in an area of the skin that is tender, bruised, red or hard.
- Use a different injection site each time you use Ustekinumab.

- If you inject too much Ustekinumab, call the healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest emergency room right away.

Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of Ustekinumab, and how to properly throw away (dispose of) used needles, syringes, and vials. The syringe, needle, and vial must never be re-used. After the rubber stopper is punctured, Ustekinumab can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of Ustekinumab.

What should I avoid while using Ustekinumab?

You should avoid receiving a live vaccine during treatment with Ustekinumab. See **"Before you use or receive Ustekinumab, tell your healthcare provider about all of your medical conditions, including if you:"**

What are the possible side effects of Ustekinumab?

Ustekinumab may cause serious side effects, including:

- See "**What is the most important information I should know about Ustekinumab?**"
- **Serious allergic reactions.** Serious allergic reactions including death can occur with Ustekinumab. Stop using Ustekinumab and get medical help right away if you get any of the following symptoms of a serious allergic reaction:
  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest discomfort
  - trouble breathing
  - skin rash
- **Posterior Reversible Encephalopathy Syndrome (PRES).** PRES is a rare condition that affects the brain and can cause death. Tell your healthcare provider right away if you get any symptoms of PRES during treatment with Ustekinumab, including:
  - headache
  - seizures
  - confusion
  - vision problems
- **Lung inflammation.** Cases of lung inflammation have happened in some people who receive Ustekinumab and may be serious. These lung problems may need to be treated in a hospital. Tell your healthcare provider right away if you develop shortness of breath or a cough that doesn't go away during treatment with Ustekinumab**.**

The most common side effects of Ustekinumab include:

- nasal congestion, sore throat, and runny nose
- upper respiratory infections
- fever
- headache
- tiredness
- itching
- nausea and vomiting
- influenza
- redness at the injection site
- vaginal yeast infections
- urinary tract infections
- sinus infection
- bronchitis
- diarrhea
- stomach pain
- joint pain

These are not all of the possible side effects of Ustekinumab. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Janssen Biotech, Inc. at 1-800-526-7736.

How should I store Ustekinumab?

- Store Ustekinumab vials and prefilled syringes in a refrigerator between 36 °F to 46 °F (2 °C to 8 °C).
- Store Ustekinumab vials standing up straight (upright).
- Store Ustekinumab in the original carton to protect it from light until time to use it.
- Do not freeze Ustekinumab.
- Do not shake Ustekinumab.
- If needed, individual Ustekinumab prefilled syringes may also be stored at room temperature up to 86 °F (30 °C) for a maximum single period of up to 30 days in the original carton to protect from light.
- Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided.
- After a prefilled syringe has been stored at room temperature, do not return it to the refrigerator.
- Throw away (discard) the prefilled syringe if it is not used within 30 days at room temperature storage.
- Do not use Ustekinumab after the expiration date on the carton or on the prefilled syringe.

Keep Ustekinumab and all medicines out of the reach of children.

General information about the safe and effective use of Ustekinumab.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Ustekinumab for a condition for which it was not prescribed. Do not give Ustekinumab to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Ustekinumab that was written for health professionals.

What are the ingredients in Ustekinumab?

Active ingredient: ustekinumab

Inactive ingredients: Single-dose prefilled syringe and single-dose vial for subcutaneous use contain L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and Sucrose.

Single-dose vial for intravenous infusion contains EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, and Sucrose.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864
For more information call 1-800-526-7736.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 4/2026

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

STELARA 130 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

Ustekinumab is a fully human IgG1κ monoclonal antibody produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is clear, colourless to light yellow, with a target pH of 6.0 and approximate osmolality of 288 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult Crohn's disease

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Paediatric Crohn's disease

STELARA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Ulcerative colitis

STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic.

4.2 Posology and method of administration

STELARA concentrate for solution for infusion is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis. STELARA concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's disease and ulcerative colitis
STELARA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table 1: Initial intravenous dose of STELARA

Body weight of patient at the time of dosing	**Recommended dose[a]**	**Number of 130 mg Vials**
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the STELARA solution for injection (vial) and solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC.

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Paediatric Crohn's disease (2 years and older)
Patients weighing less than 40 kg (BSA-based dosing)
Treatment is to be initiated with a single intravenous (IV) dose based on the patient's body surface area (BSA), see Table 2. The infusion solution is to be composed of infusion solution volume from the total number of vials of STELARA 130 mg as specified in Table 2.

Table 2: Initial intravenous dose of STELARA

BSA Range (m^2) of patient at time of dosing Body weight < 40 kg	**Recommended Dose (mg)**	**Volume of Infusion solution (mL)**	**Number of 130 mg Vials**
0.40 to <0.62	130 mg	26 mL	1 vial
0.62 to <0.95	200 mg	40 mL	2 vials
0.95 to <1.25	260 mg	52 mL	2 vials
≥1.25	325 mg	65 mL	3 vials

Patients weighing at least 40 kg (weight-based dosing)
STELARA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA 130 mg as specified in Table 3 (see section 6.6 for preparation).

Table 3: Initial intravenous dose of STELARA

Body weight of patient at the time of dosing	**Recommended dose[a]**	**Number of 130 mg Vials**
≥ 40 kg to ≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the STELARA solution

for injection (vial) and solution for injection in prefilled syringe SmPC.

The safety and efficacy of STELARA for the treatment of Crohn's disease in paediatric patients less than 2 years and less than 10 kg have not been established. No data are available.

Paediatric ulcerative colitis
The safety and efficacy of STELARA in treatment of ulcerative colitis in paediatric patients less than 18 years have not yet been established. No data are available

Method of administration
STELARA 130 mg is for intravenous use only. It should be administered over at least one hour.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics

during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (see section 4.8).

Infusion-related reactions were observed in clinical trials (see section 4.8). Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting. If a serious or life-threatening reaction is observed, appropriate therapy should be instituted and ustekinumab should be discontinued.

Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to STELARA in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with STELARA.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants,

including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations

Elderly
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Excipients with known effect

STELARA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. STELARA is however, diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

STELARA contains 10.8 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.40 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was

explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy
Data from a moderate number of prospectively collected pregnancies following exposure to STELARA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed *in utero* to ustekinumab may be increased after birth. Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

STELARA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions in the controlled periods of the adult clinical studies were nasopharyngitis (occurring in 6.9% of ustekinumab-treated patients and 5.4% of patients on placebo) and headache (occurring in 7.0% of ustekinumab-treated patients and 5.2% of patients on placebo). The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 4 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated

patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity and infusion reactions
In adult Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2.2% of 785 placebo-treated patients and 1.9% of 790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion. In the paediatric Crohn's disease study, there was one serious and one non-serious infusion reaction. Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting (see section 4.4).

Paediatric population

Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Paediatric patients 2 years and older with Crohn's disease
The safety of ustekinumab has been studied in one phase 1 and one phase 3 study of paediatric patients with moderately to severely active Crohn's disease. 34 patients in the Phase 1 study were followed up to 240 weeks and 101 patients in the Phase 3 study were followed up to 68 weeks, respectively. In general, the safety profile was similar to that seen in previous studies in adults with Crohn's disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer

(NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

In patients with ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including CRP and faecal calprotectin during the induction phase, which was maintained throughout the maintenance phase and study extension through week 200.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among STELARA-treated and control patients.

Clinical efficacy

Crohn's disease
The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development programme consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1,409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 5). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to

improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 5: Induction of clinical response and remission in UNITI-1 and UNITI-2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 6).

Table 6: Maintenance of clinical response and remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N = 131[†]**	**90 mg ustekinumab every 8 weeks N = 128[†]**	**90 mg ustekinumab every 12 weeks N = 129[†]**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002[‡]	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001[§]	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡ Patients who failed conventional therapy but not anti-TNFα therapy

§ Patients who are anti-TNFα refractory/intolerant

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's disease.

Endoscopy

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula response

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life

Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly

greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development programme consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a 44 week subcutaneous randomised withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 7). As early as week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 7: Summary of key efficacy outcomes in UNIFI-I (week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]

In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission[‡]	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	8%	21%[b]

[£] Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.

[*] Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

[§] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

[¥] A TNFα antagonist and/or vedolizumab.

[†] Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

[‡] Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

[ɟ] Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

[a] $p < 0.001$

[b] Nominally significant ($p < 0.001$)

[c] Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 8).

Table 8: Summary of key efficacy measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**90 mg ustekinumab every 8 Weeks N = 176**	**90 mg ustekinumab every 12 Weeks N = 172**
Clinical Remission**	24%	44% [a]	38% [b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85)[d]	49% (50/102)[d]
In patients who failed biological therapy[¥]	17% (15/88)	40% (36/91) [c]	23% (16/70) [d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21)[e]	23% (5/22)[e]
Maintenance of Clinical Response through week 44[§]	45%	71% [a]	68% [a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85) [c]	77% (78/102) [c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91) [c]	56% (39/70) [d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21)[e]	50% (11/22)[e]
Mucosal Healing[†]	29%	51% [a]	44% [b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40) [c]
Corticosteroid Free Clinical Remission[€]	23%	42% [a]	38% [b]
Durable Remission[ǁ]	35%	57% [c]	48% [d]
Symptomatic Remission[‡]	45%	68% [c]	62% [d]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	28%	48% [c]	41% [d]

* Following response to IV ustekinumab.
** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.
£ Maintenance of clinical remission through week 44 is defined as patients in clinical remission through week 44 among patients in clinical remission at maintenance baseline.
€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at week 44.
‖ Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to week 44 and in partial Mayo remission at last visit (week 44).
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
ǂ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p < 0.05$
[c] Nominally significant ($p < 0.001$)
[d] Nominally significant ($p < 0.05$)
[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 responders to ustekinumab induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomised to the recommended induction dose achieved clinical remission and 58% achieved clinical response at week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomised portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Study extension
In UNIFI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 400 patients who entered on and were treated with ustekinumab every 12 or 8 weeks in the study extension, symptomatic remission was generally maintained through week 200 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. Among patients who received 4 years of ustekinumab treatment and were assessed using the full Mayo score at maintenance week 200, 74.2% (69/93) and 68.3% (41/60) maintained mucosal healing and clinical remission, respectively.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 4 years of treatment in patients with ulcerative colitis.

Endoscopic normalisation
Endoscopic normalisation was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & histo-endoscopic mucosal healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44. Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 200.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalisations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalisations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalisations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with increased clearance of ustekinumab in patients with Crohn's disease or ulcerative colitis. No reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric Crohn's disease

The safety and efficacy of ustekinumab was evaluated in 101 paediatric patients 2 years and older and weighing at least 10 kg in a multicentre phase 3 study (UNITI-Jr) for paediatric patients with moderately to severely active Crohn's disease (defined by a Paediatric Crohn's Disease Activity Index [PCDAI] score >30) through 48 weeks of treatment (8 weeks of induction and 40 weeks of maintenance treatment). The study enrolled 2 patients between 2 to 5 years old and 18 patients between 6 to 11 years old; 29 patients weighed less than 40 kg, including 11 patients who weighed less than 30 kg. Patients included in the study either had not adequately responded to or had not tolerated prior biologic therapy or conventional therapy for Crohn's disease. The study included an open-label induction treatment with a single ustekinumab intravenous dose, of approximately 6 mg/kg (patients weighing at least 40 kg) or 250 mg/m^2 (patients weighing less than 40 kg, based on BSA) (see section 4.2), followed by a randomised double-blind subcutaneous maintenance regimen of 90 mg ustekinumab (patients weighing at least 40 kg) or 60 mg/m^2 (patients weighing less than 40 kg, based on BSA) (see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC) administered either every 8 weeks or every 12 weeks.

Efficacy results

The primary endpoint of the study was clinical remission at induction week 8 (defined as PCDAI score ≤ 10). The proportion of patients who achieved clinical remission was 46.5% (47/101) and is comparable to that observed in the adult ustekinumab phase 3 studies.

Clinical response was observed as early as week 3. The proportion of patients in clinical response at week 8 (defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score not more than 30) was 84.2% (85/101).

Of the 101 patients who received IV induction treatment, 97 (96.0%) entered the maintenance period of which 85 were induction responders.

Table 9 presents the analyses for the secondary endpoints through maintenance week 44.

Table 9: Summary of secondary endpoints through maintenance week 44

	90 mg or 60 mg/m^2 ustekinumab every 8 weeks N = 41	**90 mg or 60 mg/m^2 ustekinumab every 12 weeks N = 44**	**Total number of patients N = 85**
Clinical Remission [*]	48.8% (20/41)	59.1% (26/44)	54.1% (46/85)
Corticosteroid-free Clinical Remission [§]	46.3% (19/41)	59.1% (26/44)	52.9% (45/85)
Clinical remission for patients who were in clinical remission at induction week 8 [*]	73.9% (17/23)	62.5% (15/24)	68.1% (32/47)
Clinical Response [†]	56.1% (23/41)	63.6% (28/44)	60.0% (51/85)
Endoscopic response [£]	25.0% (10/40)	30.2% (13/43)	27.7% (23/83)

[*] Clinical remission is defined as PCDAI score ≤10 points.

[§] Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to maintenance week 44.

[†] Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.

[£] Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2, in patients with a baseline SES-CD score of ≥3.

Dosing frequency adjustment

Patients who entered the maintenance regimen and experienced loss of response based on PCDAI score were eligible for dose adjustment. Patients were either switched from treatment every 12 weeks to every 8 weeks or stayed on treatment every 8 weeks (sham adjustment). 2 patients were dose

adjusted to the shorter dosing interval. In these patients, clinical remission was achieved in 100% (2/2) of patients 8 weeks after dose adjustment.

Patients on both treatment regimens (treatment every 12 weeks or 8 weeks) who did not respond by maintenance week 8 or who lost response and had low levels of ustekinumab (steady state of 8-week ustekinumab trough concentration <1.4 µg/mL) were eligible to enrol in an optional Exposure Optimisation Substudy. This open-label sub study was a minimum of 16 weeks with a subcutaneous maintenance regimen of 90 mg ustekinumab or 60 mg/m^2 (based on BSA) administered every 4 weeks. A total of 26 patients enrolled in the sub study. Among participating patients, 11 (42.3%) transitioned from 12-weekly to 4-weekly dosing, and 15 (57.7%) transitioned from 8-weekly to 4-weekly dosing. At 16 weeks, after dosing frequency was changed, 95.0% (19/20) of evaluable patients were in clinical response and 50.0% (10/20) were in clinical remission.

The safety profile of the induction dose regimen and both maintenance dose regimens in the paediatric population 2 years and older is comparable with that established in the adult Crohn's disease population (see section 4.8).

Serum and faecal inflammatory biomarkers
The mean (SD) change from baseline at maintenance week 44 in C-Reactive protein (CRP) and faecal calprotectin concentrations were -6.65 (18.609) mg/L and -716.9 (2597.66) mg/kg, respectively.

Health-related quality of life
The total IMPACT-III scores and all subdomains (bowel symptoms, fatigue-related systemic symptoms, and well-being) demonstrated clinically meaningful improvements after 52 weeks.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126.1 µg/mL in patients with Crohn's disease and 127.0 µg/mL in patients with ulcerative colitis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with ulcerative colitis, Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted with intravenous ustekinumab in elderly patients.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ±20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

Paediatric population
Serum ustekinumab concentrations in paediatric patients 2 years and older and weighing at least 10 kg with Crohn's disease, were generally comparable to those in the adult Crohn's disease population.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EDTA disodium salt dihydrate
L-histidine
L-histidine monohydrochloride monohydrate
L-methionine
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. STELARA should only be diluted with sodium chloride 9 mg/mL (0.9%) solution. STELARA should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

3 years.
Do not freeze.

Chemical and physical in-use stability has been demonstrated for 8 hours at 15-25 °C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, (see section 6.3).

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a coated butyl rubber stopper. STELARA is available in a 1 vial pack.

6.6 Special precautions for disposal and other handling

The vial should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to administration. The solution is clear, colourless to light yellow. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Dilution
STELARA concentrate for solution for infusion must be diluted and prepared by a healthcare professional using aseptic technique.

1. For adult patients and paediatric patients who weigh at least 40 kg, calculate the dose and the number of STELARA vials needed based on patient weight (see section 4.2, Table 1, Table 3), or for paediatric patients who weigh less than 40 kg, calculate the dose and number of STELARA vials needed based on patient body surface area (BSA). Each 26 mL vial of STELARA contains 130 mg of ustekinumab.
2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of STELARA to be added. (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials-discard 52 mL, for 3 vials- discard 78 mL, for 4 vials- discard 104 mL)
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. For paediatric patients with Crohn's disease weighing less than 40 kg the dose is based on the patient's BSA as a single intravenous (IV) dose of STELARA. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 100 mL infusion bag equal to the volume of STELARA to be added. Withdraw the appropriate volume of STELARA from

each vial needed and add it to the 100 mL infusion bag. The final volume in the infusion bag should be 100 mL. Gently mix.
5. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
6. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
7. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometre).
8. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 19 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection
STELARA 45 mg solution for injection in pre-filled syringe
STELARA 90 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STELARA 45 mg solution for injection
Each vial contains 45 mg ustekinumab in 0.5 mL.

STELARA 45 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.

STELARA 90 mg solution for injection in pre-filled syringe
Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent, colourless to light yellow, with a target pH of 6.0 and approximate osmolality of 314 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Paediatric plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies (see section 5.1).

Psoriatic arthritis (PsA)

STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Adult Crohn's disease

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either

conventional therapy or a TNFα antagonist.

Paediatric Crohn's disease

STELARA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients from the age of 2 years and older, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Ulcerative colitis

STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic.

4.2 Posology and method of administration

STELARA is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which STELARA is indicated.

Posology

Plaque psoriasis
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy (see section 5.1, Table 5).

Psoriatic arthritis (PsA)
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established.

Paediatric plaque psoriasis (6 years and older)
The recommended dose of STELARA based on body weight is shown below (Tables 1 and 2). STELARA should be administered at weeks 0 and 4, then every 12 weeks thereafter.

Table 1 Recommended dose of STELARA for paediatric psoriasis

Body weight at the time of dosing	Recommended Dose
< 60 kg	0.75 mg/kg
≥ 60-≤ 100 kg	45 mg
> 100 kg	90 mg

To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: body weight (kg) x 0.0083 (mL/kg) or see Table 2. The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for paediatric patients who need to receive less than the full 45 mg dose.

Table 2 Injection volumes of STELARA for paediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46

56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Crohn's disease and ulcerative colitis
In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease or ulcerative colitis, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

Paediatric Crohn's disease (2 years and older)
In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

Patients weighing less than 40 kg (BSA-based dosing)
In paediatric patients with Crohn's disease weighing less than 40 kg the recommended maintenance dose is a subcutaneous dose administered based on the patient's BSA, see Table 3. The calculated volume should be rounded to the nearest 0.1 mL and administered using a 1 mL graduated syringe.

Table 3 Injection volumes for paediatric patients with Crohn's disease weighing less than 40 kg

BSA Range (m^2) of patient at time of dosing Body weight < 40 kg	**Recommended Dose (mg)**	**Volume of injection (mL)**	**Number of 45 mg/0.5 mL Vials**
0.40 to <0.62	36 mg	0.4	1 vial
0.62 to <0.95	45 mg	0.5	1 vial*
0.95 to <1.25	63 mg	0.7	2 vials
≥1.25	90 mg	1.0	2 vials*

* The pre-filled syringe (PFS) presentation may be used as an alternative to the 45 mg/0.5 mL vial for administration of the required dose

Patients weighing at least 40 kg (weight-based dosing)
In paediatric patients with Crohn's disease weighing at least 40 kg, the recommended maintenance dose is a subcutaneous 90 mg dose.

Dosing frequency in paediatric patients (2 years and older)
The first subcutaneous administration of STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Patients receiving treatment every 12 weeks who have a loss of response may increase their frequency to every 8 weeks (see sections 5.1 and 5.2). Patients receiving treatment every 12 or 8 weeks who lose response and have low ustekinumab trough levels (<1.4 µg/mL by a validated ECLIA or ELISA testing method or equivalent assay) may benefit from shortening the dosing interval to every 4 weeks if clinically indicated. A repeat trough level should be drawn at either 12 or 16 weeks after dose adjustment to every 4 weeks administration. If trough levels are >7.2 µg/mL and the patient has achieved response and is maintaining a response, the dosage interval may be changed to every 8 weeks.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after dose adjustment.

Immunomodulators, 5-aminosalicylate (5-ASA) compounds, antibiotics, and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, these medications maybe reduced or discontinued in accordance with standard of care.

The safety and efficacy of STELARA for the treatment of Crohn's disease in paediatric patients less than 2 years and less than 10 kg have not been established. No data are available.

Paediatric ulcerative colitis
The safety and efficacy of STELARA in treatment of ulcerative colitis in paediatric patients less than 18 years have not yet been established. No data are available.

Method of administration
STELARA 45 mg vials or 45 mg and 90 mg pre-filled syringes are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject STELARA if a physician determines that it is appropriate. However, the physician should ensure appropriate follow up of patients. Patients or their caregivers should be instructed to inject the prescribed amount of STELARA according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions
Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (see section 4.8).

Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to STELARA in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with STELARA.

Latex sensitivity
The needle cover on the syringe in the STELARA pre-filled syringe is manufactured from dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations

Elderly
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Excipient with known effect

STELARA contains 0.04 mg (90 mg/1.0 mL) or 0.02 mg (45 mg/0.5 mL) of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies,

concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy
Data from a moderate number of prospectively collected pregnancies following exposure to STELARA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed *in utero* to ustekinumab may be increased after birth. Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

STELARA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions in the controlled periods of the adult clinical studies were nasopharyngitis (occurring in 6.9% of ustekinumab-treated patients and 5.4% of patients on placebo) and headache (occurring in 7.0% of ustekinumab-treated patients and 5.2% of patients on placebo). The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and

phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 4 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections
In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient-years of follow-up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab-treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient-years of follow-up for ustekinumab-treated patients (69 patients in 15,165 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity reactions
During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in < 1% of patients (see section 4.4).

Paediatric population

Paediatric patients 6 years and older with plaque psoriasis
The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to

56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Paediatric patients 2 years and older with Crohn's disease
The safety of ustekinumab has been studied in one phase 1 and one phase 3 study of paediatric patients with moderately to severely active Crohn's disease. 34 patients in the Phase 1 study were followed up to 240 weeks and 101 patients in the Phase 3 study were followed up to 68 weeks, respectively. In general, the safety profile was similar to that seen in previous studies in adults with Crohn's disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

In patients with ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including CRP and faecal calprotectin during the induction phase, which was maintained throughout the maintenance phase and study extension through week 200.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among STELARA-treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)
The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at weeks 0 and 4, or ustekinumab 90 mg at weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 5 and 6).

Table 5 Summary of clinical response in psoriasis study 1 (PHOENIX 1) and psoriasis study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).

[b] PGA = Physician Global Assessment

Table 6 Summary of clinical response at week 12 in psoriasis study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.

[b] $p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of ustekinumab. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal)

($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)
Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 7 below.

Table 7 Number of patients who achieved clinical response in psoriatic arthritis study 1 (PSUMMIT I) and study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]

ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] $p < 0.001$

[b] $p < 0.05$

[c] $p = NS$

[d] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared

with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic response
Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical function and health-related quality of life
Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Crohn's disease
The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development programme consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1,409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 8). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 8: Induction of clinical response and remission in UNITI-1 and UNITI-2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission
70 point response is defined as reduction in CDAI score by at least 70 points
* Anti-TNFα failures
** Conventional therapy failures
[a] $p < 0.001$
[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 9).

Table 9: Maintenance of clinical response and remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131[†]	**90 mg ustekinumab every 8 weeks N = 128[†]**	**90 mg ustekinumab every 12 weeks N = 129[†]**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002[‡]	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001[§]	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡ Patients who failed conventional therapy but not anti-TNFα therapy

§ Patients who are anti-TNFα refractory/intolerant

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's disease.

Endoscopy

Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula response

In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life

Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly

greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Ulcerative colitis

The safety and efficacy of ustekinumab was assessed in two randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development programme consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a 44 week subcutaneous randomised withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 10). As early as week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 10: Summary of key efficacy outcomes in UNIFI-I (week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]

In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission[‡]	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	8%	21%[b]

[£] Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.

[*] Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

[§] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

[¥] A TNFα antagonist and/or vedolizumab.

[†] Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

[‡] Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

[ɟ] Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

[a] $p < 0.001$

[b] Nominally significant ($p < 0.001$)

[c] Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 11).

Table 11: Summary of key efficacy measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**90 mg ustekinumab every 8 Weeks N = 176**	**90 mg ustekinumab every 12 Weeks N = 172**
Clinical Remission**	24%	44%[a]	38%[b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85)[d]	49% (50/102)[d]
In patients who failed biological therapy[¥]	17% (15/88)	40% (36/91)[c]	23% (16/70)[d]
In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21)[e]	23% (5/22)[e]
Maintenance of Clinical Response through week 44[§]	45%	71%[a]	68%[a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85)[c]	77% (78/102)[c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91)[c]	56% (39/70)[d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21)[e]	50% (11/22)[e]
Mucosal Healing[†]	29%	51%[a]	44%[b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40)[c]
Corticosteroid Free Clinical Remission[€]	23%	42%[a]	38%[b]
Durable Remission[ǁ]	35%	57%[c]	48%[d]
Symptomatic Remission[‡]	45%	68%[c]	62%[d]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	28%	48%[c]	41%[d]

* Following response to IV ustekinumab.
** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.
§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
¥ A TNFα antagonist and/or vedolizumab.
† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.
£ Maintenance of clinical remission through week 44 is defined as patients in clinical remission through week 44 among patients in clinical remission at maintenance baseline.
€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at week 44.
‖ Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to week 44 and in partial Mayo remission at last visit (week 44).
‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
ǂ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] $p < 0.001$
[b] $p < 0.05$
[c] Nominally significant ($p < 0.001$)
[d] Nominally significant ($p < 0.05$)
[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 responders to ustekinumab induction
Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomised to the recommended induction dose achieved clinical remission and 58% achieved clinical response at week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomised portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Study extension
In UNIFI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 400 patients who entered on and were treated with ustekinumab every 12 or 8 weeks in the study extension, symptomatic remission was generally maintained through week 200 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. Among patients who received 4 years of ustekinumab treatment and were assessed using the full Mayo score at maintenance week 200, 74.2% (69/93) and 68.3% (41/60) maintained mucosal healing and clinical remission, respectively.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 4 years of treatment in patients with ulcerative colitis.

Endoscopic normalisation
Endoscopic normalisation was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & histo-endoscopic mucosal healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44. Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 200.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalisations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalisations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalisations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease or ulcerative colitis where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric plaque psoriasis
Ustekinumab has been shown to improve signs and symptoms, and health-related quality of life in paediatric patients 6 years and older with plaque psoriasis.

Adolescent patients (12-17 years)
The efficacy of ustekinumab was studied in 110 paediatric patients aged 12 to 17 years with moderate to severe plaque psoriasis in a multicentre, phase 3, randomised, double-blind, placebo-controlled study (CADMUS). Patients were randomised to receive either placebo (n = 37), or the recommended dose of ustekinumab (see section 4.2; n = 36) or half of the recommended dose of ustekinumab (n = 37) by subcutaneous injection at weeks 0 and 4 followed by every 12 week (q12w) dosing. At week 12, placebo-treated patients crossed over to receive ustekinumab.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 60% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 11% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, change from baseline in Children's Dermatology Life Quality Index (CDLQI), change from baseline in the total scale score of PedsQL (Paediatric Quality of Life Inventory) at week 12. At week 12, patients treated with ustekinumab showed significantly greater improvement in their psoriasis and health-related quality of life compared with placebo (Table 12).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) and the proportion achieving PASI 75 showed separation between the ustekinumab treated group and placebo at the first post-baseline visit at week 4, reaching a maximum by week 12. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through week 52 (Table 12).

Table 12: Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS) (Age 12-17)			
	Week 12		**Week 52**
	Placebo	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)	N (%)
Patients randomised	37	36	35
PGA			
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]	20 (57.1%)
PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]	13 (37.1%)
PASI			
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]	28 (80.0%)
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]	23 (65.7%)
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]	13 (37.1%)
CDLQI			
CDLQI of 0 or 1[b]	6 (16.2%)	18 (50.0%)[c]	20 (57.1%)
PedsQL			
Change from baseline Mean (SD)[d]	3.35 (10.04)	8.03 (10.44)[e]	7.26 (10.92)

[a] $p < 0.001$

[b] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

[c] $p = 0.002$

[d] PedsQL: The PedsQL Total Scale Score is a general health-related quality of life measure developed for use in children and adolescent populations. For the placebo group at week 12, N = 36

[e] $p = 0.028$

During the placebo-controlled period through week 12, the efficacy of both the recommended and half of the recommended dose groups were generally comparable at the primary endpoint (69.4% and 67.6% respectively) although there was evidence of a dose response for higher level efficacy criteria (e.g. PGA of cleared (0), PASI 90). Beyond week 12, efficacy was generally higher and better sustained in the recommended dose group compared with half of the recommended dosage group in which a modest loss of efficacy was more frequently observed toward the end of each 12 week dosing interval. The safety profiles of the recommended dose and half of the recommended dose were comparable.

Children (6-11 years)
The efficacy of ustekinumab was studied in 44 paediatric patients aged 6 to 11 years with moderate to severe plaque psoriasis in an open label, single-arm, multicentre, phase 3, study (CADMUS Jr.). Patients were treated with the recommended dose of ustekinumab (see section 4.2; n = 44) by subcutaneous injection at weeks 0 and 4 followed by every 12 week (q12w) dosing.

Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 43% of the patients had prior exposure to conventional systemic therapy or phototherapy. Approximately 5% of the patients had prior exposure to biologics.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at week 12. Secondary endpoints included PASI 75, PASI 90, and change from baseline in Children's Dermatology Life Quality Index (CDLQI) at week 12. At week 12, patients treated with ustekinumab showed clinically meaningful improvements in their psoriasis and health-related quality of life (Table 13).

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) at week 12 was 77.3%. Efficacy (defined as PGA 0 or 1) was observed as early as the first post-baseline visit at week 4 and the proportion of subjects who achieved a PGA score of 0 or 1 increased through week 16 and then remained relatively stable through week 52. Improvements in PGA, PASI, and CDLQI were maintained through week 52 (Table 13).

Table 13 Summary of primary and secondary endpoints at week 12 and week 52

Paediatric psoriasis study (CADMUS Jr.) (Age 6-11)		
	Week 12	**Week 52**
	Recommended dose of Ustekinumab	Recommended dose of Ustekinumab
	N (%)	N (%)
Patients enrolled	44	41
PGA		
PGA of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI		
PASI 75 responders	37 (84.1%)	36 (87.8%)
PASI 90 responders	28 (63.6%)	29 (70.7%)
PASI 100 responders	15 (34.1%)	22 (53.7%)

CDLQI[a]		
Patients with a CDLQI > 1 at baseline	(N=39)	(N=36)
CDLQI of 0 or 1	24 (61.5%)	21 (58.3%)

[a] CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the paediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

Paediatric Crohn's disease

The safety and efficacy of ustekinumab was evaluated in 101 paediatric patients 2 years and older and weighing at least 10 kg in a multicentre phase 3 study (UNITI-Jr) for paediatric patients with moderately to severely active Crohn's disease (defined by a Paediatric Crohn's Disease Activity Index [PCDAI] score >30) through 48 weeks of treatment (8 weeks of induction and 40 weeks of maintenance treatment). The study enrolled 2 patients between 2 to 5 years old and 18 patients between 6 to 11 years old; 29 patients weighed less than 40 kg, including 11 patients who weighed less than 30 kg. Patients included in the study either had not adequately responded to or had not tolerated prior biologic therapy or conventional therapy for Crohn's disease. The study included an open-label induction treatment with a single ustekinumab intravenous dose, of approximately 6 mg/kg (patients weighing at least 40 kg) or 250 mg/m^2 (patients weighing less than 40 kg, based on BSA) (see section 4.2), followed by a randomised double-blind subcutaneous maintenance regimen of 90 mg ustekinumab (patients weighing at least 40 kg) or 60 mg/m^2 (patients weighing less than 40 kg, based on BSA) (see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection pre-filled syringe SmPC) administered either every 8 weeks or every 12 weeks.

Efficacy results

The primary endpoint of the study was clinical remission at induction week 8 (defined as PCDAI score ≤ 10). The proportion of patients who achieved clinical remission was 46.5% (47/101) and is comparable to that observed in the adult ustekinumab phase 3 studies.

Clinical response was observed as early as week 3. The proportion of patients in clinical response at week 8 (defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score not more than 30) was 84.2% (85/101).

Of the 101 patients who received IV induction treatment, 97 (96.0%) entered the maintenance period of which 85 were induction responders.

Table 14 presents the analyses for the secondary endpoints through maintenance week 44.

Table 14: Summary of secondary endpoints through maintenance week 44

	90 mg or 60 mg/m^2 ustekinumab every 8 weeks N = 41	**90 mg or 60 mg/m^2 ustekinumab every 12 weeks N = 44**	**Total number of patients N = 85**
Clinical Remission [*]	48.8% (20/41)	59.1% (26/44)	54.1% (46/85)
Corticosteroid-free Clinical Remission [§]	46.3% (19/41)	59.1% (26/44)	52.9% (45/85)
Clinical remission for patients who were in clinical remission at induction week 8 [*]	73.9% (17/23)	62.5% (15/24)	68.1% (32/47)
Clinical Response [†]	56.1% (23/41)	63.6% (28/44)	60.0% (51/85)
Endoscopic response [£]	25.0% (10/40)	30.2% (13/43)	27.7% (23/83)

[*] Clinical remission is defined as PCDAI score ≤10 points.

[§] Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to maintenance week 44.

[†] Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.

£ Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2, in patients with a baseline SES-CD score of ≥3.

Dosing frequency adjustment
Patients who entered the maintenance regimen and experienced loss of response based on PCDAI score were eligible for dose adjustment. Patients were either switched from treatment every 12 weeks to every 8 weeks or stayed on treatment every 8 weeks (sham adjustment). 2 patients were dose adjusted to the shorter dosing interval. In these patients, clinical remission was achieved in 100% (2/2) of patients 8 weeks after dose adjustment.

Patients on both treatment regimens (treatment every 12 weeks or 8 weeks) who did not respond by maintenance week 8 or who lost response and had low levels of ustekinumab (steady state of 8-week ustekinumab trough concentration <1.4 µg/mL) were eligible to enrol in an optional Exposure Optimisation Substudy. This open-label sub study was a minimum of 16 weeks with a subcutaneous maintenance regimen of 90 mg ustekinumab or 60 mg/m^2 (based on BSA) administered every 4 weeks. A total of 26 patients enrolled in the sub study. Among participating patients, 11 (42.3%) transitioned from 12-weekly to 4-weekly dosing, and 15 (57.7%) transitioned from 8-weekly to 4-weekly dosing. At 16 weeks, after dosing frequency was changed, 95.0 % (19/20) of evaluable patients were in clinical response and 50.0% (10/20) were in clinical remission.

The safety profile of the induction dose regimen and both maintenance dose regimens in the paediatric population 2 years and older is comparable with that established in the adult Crohn's disease population (see section 4.8).

Serum and faecal inflammatory biomarkers
The mean (SD) change from baseline at maintenance week 44 in C-Reactive protein (CRP) and faecal calprotectin concentrations were -6.65 (18.609) mg/L and -716.9 (2597.66) mg/kg, respectively.

Health-related quality of life
The total IMPACT-III scores and all subdomains (bowel symptoms, fatigue-related systemic symptoms, and well-being) demonstrated clinically meaningful improvements after 52 weeks.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in juvenile idiopathic arthritis and ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 µg/mL to 0.26 µg/mL (45 mg) and from 0.47 µg/mL to 0.49 µg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease and ulcerative colitis, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 µg/mL to 2.24 µg/mL and from 0.61 µg/mL to 0.76 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. In patients with ulcerative colitis, median steady-state trough concentrations ranged from 2.69 µg/mL to 3.09 µg/mL and from 0.92 µg/mL to 1.19 µg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease and ulcerative colitis, based on observed data and population PK analyses, randomised subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations, and clinical remission and mucosal healing.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

The bioavailability of ustekinumab following administration by syringe or pre-filled pen was comparable.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

Paediatric population

Serum ustekinumab concentrations in paediatric psoriasis patients 6 to 17 years of age, treated with the recommended weight-based dose were generally comparable to those in the adult psoriasis population treated with the adult dose. Serum ustekinumab concentrations in paediatric psoriasis patients 12-17 years of age (CADMUS) treated with half of the recommended weight-based dose were generally lower than those in adults.

The steady-state serum concentrations in paediatric patients with Crohn's disease 2 years and older and weighing at least 10 kg were comparable to those in the adult Crohn's disease population.

Patients who had loss of response and low ustekinumab levels were dose adjusted to maintenance treatment every 4 weeks. Serum ustekinumab concentrations increased following dose escalation and were within the range of the concentrations at the approved recommended dose in adults treated every 8 weeks.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No

adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

STELARA 45 mg solution for injection
2 years

STELARA 45 mg solution for injection in pre-filled syringe
3 years

STELARA 90 mg solution for injection in pre-filled syringe
3 years

Individual pre-filled syringes may be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a syringe has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial or pre-filled syringe in the outer carton in order to protect from light.
If needed, individual pre-filled syringes may be stored at room temperature up to 30°C (see section 6.3).

6.5 Nature and contents of container

<u>STELARA 45 mg solution for injection</u>
0.5 mL solution in a type I glass 2 mL vial closed with a coated butyl rubber stopper.

STELARA 45 mg solution for injection in pre-filled syringe
0.5 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle cover containing dry natural rubber (a derivative of latex). The syringe is fitted with a passive safety guard.

STELARA 90 mg solution for injection in pre-filled syringe
1 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle cover containing dry natural rubber (a derivative of latex). The syringe is fitted with a passive safety guard.

STELARA is available in a 1 vial pack or a pack of 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

The vial or pre-filled syringe should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

STELARA does not contain preservatives; therefore any unused medicinal product remaining in the vial and the syringe should not be used. STELARA is supplied as a sterile, single-use vial or single-use pre-filled syringe. The syringe, needle and vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

When using the single-dose vial, a 1 mL syringe with a 27 gauge, ½ inch (13 mm) needle is recommended.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

STELARA 45 mg solution for injection
EU/1/08/494/001

STELARA 45 mg solution for injection in pre-filled syringe
EU/1/08/494/003

STELARA 90 mg solution for injection in pre-filled syringe
EU/1/08/494/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 19 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection in pre-filled pen
STELARA 90 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STELARA 45 mg solution for injection in pre-filled pen
Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL.

STELARA 90 mg solution for injection in pre-filled pen
Each pre-filled pen contains 90 mg ustekinumab in 1 mL.

Ustekinumab is a fully human IgG1κ monoclonal antibody produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent, colourless to light yellow, with a target pH of 6.0 and approximate osmolality of 314 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate (MTX) or PUVA (psoralen and ultraviolet A) (see section 5.1).

Psoriatic arthritis (PsA)

STELARA, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate (see section 5.1).

Crohn's disease

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Ulcerative colitis

STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic.

4.2 Posology and method of administration

STELARA is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of conditions for which STELARA is indicated.

Posology

Plaque psoriasis
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. (see section 5.1, Table 4).

Psoriatic arthritis (PsA)
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population
The safety and efficacy of STELARA in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established. The pre-filled pen has not been studied in the paediatric population and is not recommended for use in paediatric patients. See section 4.2 of the pre-filled syringe SmPC for posology and method of administration in paediatric patients 6 years and older with psoriasis.

Crohn's disease and ulcerative colitis
In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1, section 5.2).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease or Ulcerative Colitis, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly
No dose adjustment is needed for elderly patients (≥ 65 years) (see section 4.4).

Renal and hepatic impairment
STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

The safety and efficacy of STELARA for the treatment of Crohn's disease in paediatric patients less than 2 years or ulcerative colitis in children less than 18 years have not yet been established. No data are available. The pre-filled pen has not been studied in the paediatric population and is not recommended for use in paediatric patients. See section 4.2 of the Concentrate for solution for infusion and pre-filled syringe SmPC for posology and method of administration in paediatric patients 2 years and older with Crohn's disease.

Method of administration
STELARA 45 mg and 90 mg pre-filled pens are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject STELARA if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients or their caregivers should be instructed to inject the prescribed amount of STELARA according to the directions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies

Immunosuppressants like ustekinumab have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions

Serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of STELARA should be discontinued (see section 4.8).

Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events

Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to STELARA in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with STELARA.

Latex sensitivity

The needle cover inside the bottom cap of the pre-filled pen is manufactured from dry natural rubber

(a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
STELARA has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether STELARA may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations

Elderly
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently

from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Excipient with known effect

STELARA contains 0.04 mg (90 mg/1.0 mL) or 0.02 mg (45 mg/0.5 mL) of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of STELARA. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of STELARA (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy
Data from a moderate number of prospectively collected pregnancies following exposure to STELARA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3).

However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed *in utero* to ustekinumab may be increased after birth.
Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

Breast-feeding
Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

Fertility
The effect of ustekinumab on human fertility has not been evaluated (see section 5.3).

4.7 Effects on ability to drive and use machines

STELARA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions in the controlled periods of the adult clinical studies were nasopharyngitis (occurring in 6.9% of ustekinumab-treated patients and 5.4% of patients on placebo) and headache (occurring in 7.0% of ustekinumab-treated patients and 5.2% of patients on placebo). The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions
The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 1 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by System Organ Class and frequency, using the following convention: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

System Organ Class	Frequency: Adverse reaction
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common : Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

* See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions

Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient-year of follow-up in ustekinumab-treated patients, and the rate of serious infections was 0.02 per patient-year of follow-up in ustekinumab-treated patients (289 serious infections in 15,227 patient-years of follow-up) and serious infections reported included pneumonia, anal abscess,

cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient-years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding nonmelanoma skin cancers were reported in 76 patients in 15,205 patient years of follow up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab treated patients). The incidence of malignancies reported in ustekinumab-treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than nonmelanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of nonmelanoma skin cancer was 0.46 per 100 patient-years of follow up for ustekinumab-treated patients (69 patients in 15,165 patient years of follow up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity reactions
During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of ustekinumab, rash and urticaria have each been observed in <1% of patients (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 6 mg/kg have been administered intravenously in clinical studies without dose-limiting toxicity. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor

protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

In patients with ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including CRP and faecal calprotectin during the induction phase, which was maintained throughout the maintenance phase and study extension through week 200.

Immunisation

During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with STELARA for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among STELARA-treated and control patients.

Clinical efficacy

Plaque psoriasis (Adults)

The safety and efficacy of ustekinumab was assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy. In addition, a randomised, blinded assessor, active-controlled study compared ustekinumab and etanercept in patients with moderate to severe plaque psoriasis who had had an inadequate response to, intolerance to, or contraindication to ciclosporin, MTX, or PUVA.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1,230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at weeks 0 and 4 crossed over to receive

ustekinumab (either 45 mg or 90 mg) at weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (ACCEPT) evaluated 903 patients with moderate to severe psoriasis who inadequately responded to, were intolerant to, or had a contraindication to other systemic therapy and compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept. During the 12-week active-controlled portion of the study, patients were randomised to receive etanercept (50 mg twice a week), ustekinumab 45 mg at weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4.

Baseline disease characteristics were generally consistent across all treatment groups in Psoriasis Studies 1 and 2 with a median baseline PASI score from 17 to 18, median baseline Body Surface Area (BSA) ≥ 20, and median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (Psoriasis Study 1) and one quarter (Psoriasis Study 2) of subjects had Psoriatic Arthritis (PsA). Similar disease severity was also seen in Psoriasis Study 3.

The primary endpoint in these studies was the proportion of patients who achieved PASI 75 response from baseline at week 12 (see Tables 2 and 3).

Table 2: Summary of clinical response in psoriasis study 1 (PHOENIX 1) and psoriasis study 2 (PHOENIX 2)

	Week 12 2 doses (week 0 and week 4)			Week 28 3 doses (week 0, week 4 and week 16)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%)[a]	220 (86%)[a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%)[a]	170 (66%)[a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%)[a]	94 (37%)[a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%)[a]	156 (61%)[a]	146 (58%)	160 (66%)
Number of patients ≤ 100 kg	166	168	164	164	153
PASI 75 response N (%)	6 (4%)	124 (74%)	107 (65%)	130 (79%)	124 (81%)
Number of patients > 100 kg	89	87	92	86	90
PASI 75 response N (%)	2 (2%)	47 (54%)	63 (68%)	48 (56%)	67 (74%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%)[a]	367 (89%)[a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%)[a]	311 (76%)[a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%)[a]	209 (51%)[a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%)[a]	300 (73%)[a]	241 (61%)	279 (70%)
Number of patients ≤ 100 kg	290	297	289	287	280
PASI 75 response N (%)	12 (4%)	218 (73%)	225 (78%)	217 (76%)	226 (81%)
Number of patients > 100 kg	120	112	121	110	119
PASI 75 response N (%)	3 (3%)	55 (49%)	86 (71%)	59 (54%)	88 (74%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with placebo (PBO).

[b] PGA = Physician Global Assessment

Table 3: Summary of clinical response at week 12 in psoriasis study 3 (ACCEPT)

	Psoriasis Study 3		
	Etanercept 24 doses (50 mg twice a week)	Ustekinumab 2 doses (week 0 and week 4)	
		45 mg	90 mg
Number of patients randomised	347	209	347
PASI 50 response N (%)	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response N (%)	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response N (%)	80 (23%)	76 (36%)[a]	155 (45%)[a]
PGA of cleared or minimal N (%)	170 (49%)	136 (65%)[a]	245 (71%)[a]
Number of patients ≤ 100 kg	251	151	244
PASI 75 response N (%)	154 (61%)	109 (72%)	189 (77%)
Number of patients > 100 kg	96	58	103
PASI 75 response N (%)	43 (45%)	32 (55%)	67 (65%)

[a] $p < 0.001$ for ustekinumab 45 mg or 90 mg in comparison with etanercept.

[b] $p = 0.012$ for ustekinumab 45 mg in comparison with etanercept.

In Psoriasis Study 1 maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of ustekinumab. At 1 year (week 52), 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At 18 months (week 76), 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal). At 3 years (week 148), 82% of patients re-randomised to maintenance treatment were PASI 75 responders. At 5 years (week 244), 80% of patients re-randomised to maintenance treatment were PASI 75 responders.

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at week 2 and week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at week 4 and 12, which were sustained through week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo. In Psoriasis Study 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo.

Psoriatic arthritis (PsA) (Adults)

Ustekinumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

The safety and efficacy of ustekinumab was assessed in 927 patients in two randomised, double-blind, placebo-controlled studies in patients with active PsA (≥ 5 swollen joints and ≥ 5 tender joints) despite nonsteroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these studies had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively. Patients were randomised to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at weeks 0 and 4 followed by

every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤ 25 mg/week).

In PsA Study 1 (PSUMMIT I) and PsA Study 2 (PSUMMIT II), 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In Study 1 previous treatment with anti-tumour necrosis factor (TNF)α agent was not allowed. In Study 2, the majority of patients (58%, n = 180) had been previously treated with one or more anti-TNFα agent(s), of whom over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance at any time.

Signs and symptoms
Treatment with ustekinumab resulted in significant improvements in the measures of disease activity compared to placebo at week 24. The primary endpoint was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at week 24. The key efficacy results are shown in Table 4 below.

Table 4 Number of patients who achieved clinical response in psoriatic arthritis study 1 (PSUMMIT I) and study 2 (PSUMMIT II) at week 24

	Psoriatic arthritis Study 1			**Psoriatic arthritis Study 2**		
	PBO	**45 mg**	**90 mg**	**PBO**	**45 mg**	**90 mg**
Number of patients randomised	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)[a]	101 (50%)[a]	21 (20%)	45 (44%)[a]	46 (44%)[a]
ACR 50 response, N (%)	18 (9%)	51 (25%)[a]	57 (28%)[a]	7 (7%)	18 (17%)[b]	24 (23%)[a]
ACR 70 response, N (%)	5 (2%)	25 (12%)[a]	29 (14%)[a]	3 (3%)	7 (7%)[c]	9 (9%)[c]
Number of patients with ≥ 3% BSA[d]	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)[a]	93 (62%)[a]	4 (5%)	41 (51%)[a]	45 (56%)[a]
PASI 90 response, N (%)	4 (3%)	60 (41%)[a]	65 (44%)[a]	3 (4%)	24 (30%)[a]	36 (44%)[a]
Combined PASI 75 and ACR 20 response, N (%)	8 (5%)	40 (28%)[a]	62 (42%)[a]	2 (3%)	24 (30%)[a]	31 (38%)[a]
Number of patients ≤ 100 kg	154	153	154	74	74	73
ACR 20 response, N (%)	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
Number of patients with ≥ 3% BSA[d]	105	105	111	54	58	57
PASI 75 response, N (%)	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
Number of patients > 100 kg	52	52	50	30	29	31
ACR 20 response, N (%)	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
Number of patients with ≥ 3% BSA[d]	41	40	38	26	22	24
PASI 75 response, N (%)	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)

[a] $p < 0.001$
[b] $p < 0.05$
[c] p = NS
[d] Number of patients with ≥ 3% BSA psoriasis skin involvement at baseline

ACR 20, 50 and 70 responses continued to improve or were maintained through week 52 (PsA Study 1 and 2) and week 100 (PsA Study 1). In PsA Study 1, ACR 20 responses at week 100 were achieved by 57% and 64%, for 45 mg and 90 mg, respectively. In PsA Study 2, ACR 20 responses at week 52 were achieved by 47% and 48%, for 45 mg and 90 mg, respectively.

The proportion of patients achieving a modified PsA response criteria (PsARC) response was also significantly greater in the ustekinumab groups compared to placebo at week 24. PsARC responses were maintained through weeks 52 and 100. A higher proportion of patients treated with ustekinumab who had spondylitis with peripheral arthritis as their primary presentation, demonstrated 50 and 70 percent improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared with placebo at week 24.

Responses observed in the ustekinumab treated groups were similar in patients receiving and not receiving concomitant MTX, and were maintained through weeks 52 and 100. Patients previously treated with anti-TNFα agents who received ustekinumab achieved a greater response at week 24 than patients receiving placebo (ACR 20 response at week 24 for 45 mg and 90 mg was 37% and 34%, respectively, compared with placebo 15%; $p < 0.05$), and responses were maintained through week 52.

For patients with enthesitis and/or dactylitis at baseline, in PsA Study 1 significant improvement in enthesitis and dactylitis score was observed in the ustekinumab groups compared with placebo at week 24. In PsA Study 2 significant improvement in enthesitis score and numerical improvement (not statistically significant) in dactylitis score was observed in the ustekinumab 90 mg group compared with placebo at week 24. Improvements in enthesitis score and dactylitis score were maintained through weeks 52 and 100.

Radiographic response
Structural damage in both hands and feet was expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PsA Study 1 and 2 was performed. Ustekinumab demonstrated a statistically significant decrease in the rate of progression of structural damage compared to placebo, as measured by change from baseline to week 24 in the total modified vdH-S score (mean ± SD score was 0.97 ± 3.85 in the placebo group compared with 0.40 ± 2.11 and 0.39 ± 2.40 in the ustekinumab 45 mg ($p < 0.05$) and 90 mg ($p < 0.001$) groups, respectively). This effect was driven by PsA Study 1. The effect is considered demonstrated irrespective of concomitant MTX use, and was maintained through weeks 52 (integrated analysis) and 100 (PsA Study 1).

Physical function and health-related quality of life
Ustekinumab-treated patients showed significant improvement in physical function as assessed by the Disability Index of the Health Assessment Questionnaire (HAQ-DI) at week 24. The proportion of patients achieving a clinically meaningful ≥ 0.3 improvement in HAQ-DI score from baseline was also significantly greater in the ustekinumab groups when compared with placebo. Improvement in HAQ-DI score from baseline was maintained through weeks 52 and 100.

There was significant improvement in DLQI scores in the ustekinumab groups as compared with placebo at week 24, which was maintained through weeks 52 and 100. In PsA Study 2 there was a significant improvement in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores in the ustekinumab groups when compared with placebo at week 24. The proportion of patients achieving a clinically significant improvement in fatigue (4 points in FACIT-F) was also significantly greater in the ustekinumab groups compared with placebo. Improvements in FACIT scores were maintained through week 52.

Crohn's disease
The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development programme consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed

by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1,409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNFα therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 5). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 5: Induction of clinical response and remission in UNITI-1 and UNITI 2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 6).

Table 6: Maintenance of clinical response and remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N = 131†**	**90 mg ustekinumab every 8 weeks** **N = 128†**	**90 mg ustekinumab every 12 weeks** **N = 129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy.

‡ Patients who failed conventional therapy but not anti-TNFα therapy.

§ Patients who are anti-TNFα refractory/intolerant.

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo-colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo. Improvement in health-related quality of life was generally maintained during the extension through week 252.

Ulcerative colitis
The safety and efficacy of ustekinumab was assessed in two randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2). The clinical development programme consisted of one intravenous induction study (referred to as UNIFI-I) with treatment of up to 16 weeks followed by a 44 week subcutaneous randomised withdrawal maintenance study (referred to as UNIFI-M) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-I and UNIFI-M were based on central review of endoscopies.

UNIFI-I included 961 patients. The primary endpoint for the induction study was the proportion of subjects in clinical remission at week 8. Patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Concomitant doses of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-I a significantly greater proportion of patients were in clinical remission in the ustekinumab treated group compared to placebo at week 8 (Table 7). As early as week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as week 2.

Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 7: Summary of key efficacy outcomes in UNIFI-I (week 8)

	Placebo N = 319	**Recommended dose of ustekinumab£ N = 322**
Clinical Remission*	5%	16%[a]
In patients who failed conventional therapy, but not a biologic	9% (15/158)	19% (29/156)[c]
In patients who failed biological therapy¥	1% (2/161)	13% (21/166)[b]
In patients who failed both a TNF and vedolizumab	0% (0/47)	10% (6/58)[c]
Clinical Response§	31%	62%[a]
In patients who failed conventional therapy, but not a biologic	35% (56/158)	67% (104/156)[b]
In patients who failed biological therapy¥	27% (44/161)	57% (95/166)[b]
In patients who failed both a TNF and vedolizumab	28% (13/47)	52% (30/58)[c]
Mucosal Healing†	14%	27%[a]
In patients who failed conventional therapy, but not a biologic	21% (33/158)	33% (52/156)[c]
In patients who failed biological therapy	7% (11/161)	21% (35/166)[b]
Symptomatic Remission‡	23%	45%[b]
Combined Symptomatic Remission and Mucosal Healing⸸	8%	21%[b]

£ Infusion dose of ustekinumab using the weight-based dosage regimen specified in *Table 1*.

* Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

⸸ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

[a] $p < 0.001$

[b] Nominally significant ($p < 0.001$)

[c] Nominally significant ($p < 0.05$)

UNIFI-M, evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-I. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the STELARA Solution for injection (vial) and Solution for injection in pre-filled syringe SmPC or pre-filled pen SmPC).

Significantly greater proportions of patients were in clinical remission in both ustekinumab treated groups compared to the placebo group at week 44 (see Table 8).

Table 8: Summary of key efficacy measures in UNIFI-M (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 175	**90 mg ustekinumab every 8 Weeks N = 176**	**90 mg ustekinumab every 12 Weeks N = 172**
Clinical Remission**	24%	44%[a]	38%[b]
In patients who failed conventional therapy, but not a biologic	31% (27/87)	48% (41/85)[d]	49% (50/102)[d]
In patients who failed biological therapy¥	17% (15/88)	40% (36/91)[c]	23% (16/70)[d]

In patients who failed both a TNF and vedolizumab	15% (4/27)	33% (7/21)[e]	23% (5/22)[e]
Maintenance of Clinical Response through week 44[§]	45%	71%[a]	68%[a]
In patients who failed conventional therapy, but not a biologic	51% (44/87)	78% (66/85)[c]	77% (78/102)[c]
In patients who failed biological therapy[¥]	39% (34/88)	65% (59/91)[c]	56% (39/70)[d]
In patients who failed both a TNF and vedolizumab	41% (11/27)	67% (14/21)[e]	50% (11/22)[e]
Mucosal Healing[†]	29%	51%[a]	44%[b]
Maintenance of Clinical Remission through week 44[£]	38% (17/45)	58% (22/38)	65% (26/40)[c]
Corticosteroid Free Clinical Remission[€]	23%	42%[a]	38%[b]
Durable Remission[‖]	35%	57%[c]	48%[d]
Symptomatic Remission[‡]	45%	68%[c]	62%[d]
Combined Symptomatic Remission and Mucosal Healing[ɟ]	28%	48%[c]	41%[d]

* Following response to IV ustekinumab.

** Clinical remission is defined as Mayo score ≤2 points, with no individual subscore > 1.

§ Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

¥ A TNFα antagonist and/or vedolizumab.

† Mucosal healing is defined as a Mayo endoscopic sub-score of 0 or 1.

£ Maintenance of clinical remission through week 44 is defined as patients in clinical remission through week 44 among patients in clinical remission at maintenance baseline.

€ Corticosteroid-free clinical remission is defined as patients in clinical remission and not receiving corticosteroids at week 44.

‖ Durable Remission is defined as partial Mayo remission at ≥80% of all visits prior to week 44 and in partial Mayo remission at last visit (week 44).

‡ Symptomatic remission is defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

ɟ Combined symptomatic remission and mucosal healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

[a] $p < 0.001$

[b] $p < 0.05$

[c] Nominally significant ($p < 0.001$)

[d] Nominally significant ($p < 0.05$)

[e] Not statistically significant

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy including in patients with a primary non-response to TNFα antagonist therapy. A beneficial effect was also observed in induction in patients who failed at least one prior TNFα antagonist therapy and vedolizumab, however the number of patients in this subgroup was too small to draw definitive conclusions about the beneficial effect in this group during maintenance.

Week 16 responders to ustekinumab induction

Ustekinumab treated patients who were not in response at week 8 of UNIFI-I received an administration of 90 mg SC ustekinumab at week 8 (36% of patients). Of those patients, 9% of patients who were initially randomised to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNFI-I study but were in response at week 16 (157 patients) entered into the non-randomised portion of UNIFI-M and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 30% achieved remission at week 44.

Study extension
In UNIFI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 400 patients who entered on and were treated with ustekinumab every 12 or 8 weeks in the study extension, symptomatic remission was generally maintained through week 200 for patients who failed conventional therapy (but not a biologic therapy) and those who failed biologic therapy, including those who failed both anti-TNF and vedolizumab. Among patients who received 4 years of ustekinumab treatment and were assessed using the full Mayo score at maintenance week 200, 74.2% (69/93) and 68.3% (41/60) maintained mucosal healing and clinical remission, respectively.

The safety analysis including 457 patients (1289.9 person-years) followed up to 220 weeks showed a safety profile between week 44 and 220 that was comparable with that observed up to week 44.

No new safety concerns were identified in this study extension with up to 4 years of treatment in patients with ulcerative colitis.

Endoscopic normalisation
Endoscopic normalisation was defined as a Mayo endoscopic subscore of 0 and was observed as early as week 8 of UNIFI-I. At week 44 of UNIFI-M, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & histo-endoscopic mucosal healing
Histologic healing (defined as neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at week 8 of UNIFI-I and week 44 of UNIFI-M. At week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At week 44 maintenance of this effect was observed with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-I and week 44 of UNIFI-M. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires.

At week 8 of UNIFI-I, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-M through week 44. Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 200.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalisations and ulcerative colitis (UC) related surgeries
Through week 8 of UNIFI-I, the proportions of subjects with UC disease related hospitalisations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared

with subjects in the placebo group (4.4%, 14/319) and no subjects underwent UC disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through week 44 of UNIFI-M, a significantly lower number of UC-related hospitalisations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent UC disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through week 44.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with both increased clearance and reduced efficacy of ustekinumab, except in patients with Crohn's disease or ulcerative colitis where no reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in ulcerative colitis and juvenile idiopathic arthritis. The pre-filled pen has not been studied in the paediatric population and is not recommended for use by paediatric patients.

5.2 Pharmacokinetic properties

Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to those observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses
Serum concentration time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady state serum concentrations of ustekinumab were achieved by week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. The median steady state trough concentration ranged from 0.21 μg/mL to 0.26 μg/mL (45 mg) and from 0.47 μg/mL to 0.49 μg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease and ulcerative colitis, following an intravenous dose of ~6 mg/kg, starting at week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. In patients with Crohn's disease, median steady-state trough concentrations ranged from 1.97 μg/mL to 2.24 μg/mL and from 0.61 μg/mL to 0.76 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively. In patients with ulcerative colitis, median steady-state trough concentrations ranged from 2.69 μg/mL to 3.09 μg/mL and from 0.92 μg/mL to 1.19 μg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady-state trough levels following 90 mg every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis using data from patients with psoriasis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. The median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

Dosing frequency adjustment
In patients with Crohn's disease and ulcerative colitis, based on observed data and population PK analyses, randomised subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations, and clinical remission and mucosal healing.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function.
No specific studies have been conducted in elderly patients.

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis and ulcerative colitis.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ± 20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

The bioavailability of ustekinumab following administration by syringe or pre-filled pen was comparable.

The pre-filled pen has not been studied in the paediatric population and is not recommended for use by paediatric patients.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

STELARA 45 mg solution for injection in pre-filled pen
3 years

STELARA 90 mg solution for injection in pre-filled pen
3 years

Individual pre-filled pens may be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a pre-filled pen has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the pre-filled pen if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
If needed, individual pre-filled pens may be stored at room temperature up to 30°C (see section 6.3).

6.5 Nature and contents of container

STELARA 45 mg solution for injection in pre-filled pen
0.5 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle assembled in a pre-filled pen with a passive needle guard. The needle cover inside the bottom cap of the pre-filled pen contains dry natural rubber (a derivative of latex).

STELARA 90 mg solution for injection in pre-filled pen
1 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle assembled in a pre-filled pen with a passive needle guard. The needle cover inside the bottom cap of the pre-filled pen contains dry natural rubber (a derivative of latex).

STELARA is available in a pack of 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

The pre-filled pen should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to subcutaneous administration. The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach room temperature (approximately half an hour). Detailed instructions for use are provided in the package leaflet.

STELARA does not contain preservatives; therefore any unused medicinal product remaining in the pre-filled pen should not be used. STELARA is supplied as a sterile, single-use pre-filled pen. The pre-filled pen must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

STELARA 45 mg solution for injection in pre-filled pen
EU/1/08/494/006

STELARA 90 mg solution for injection in pre-filled pen
EU/1/08/494/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2009
Date of latest renewal: 19 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency:
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (130 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 130 mg concentrate for solution for infusion
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 130 mg of ustekinumab in 26 mL.

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
130 mg/26 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Read the package leaflet before use.
For single use only.
Intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including in Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (130 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 130 mg concentrate for solution for infusion
ustekinumab
For IV use after dilution.

2. METHOD OF ADMINISTRATION

Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

130 mg/26 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 45 mg solution for injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature: _____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 30 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection in pre-filled syringe
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
90 mg/1 mL
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature: _____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 30 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 90 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection in pre-filled pen
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 45 mg of ustekinumab in 0.5 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 mL
1 pre-filled pen
Single-dose pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

OPEN HERE
Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature:_____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 30 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON



Read Instructions for Use in full before use.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 45 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection in pre-filled pen
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 90 mg of ustekinumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections. The container of this medicinal product contains latex rubber. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
90 mg/1 mL
1 pre-filled pen
Single-dose pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

OPEN HERE
Do not shake.
Subcutaneous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard date, if stored at room temperature: _____

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 30 days, but not exceeding the original expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/494/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 90 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON



Read Instructions for Use in full before use.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

STELARA 90 mg injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

STELARA 130 mg concentrate for solution for infusion
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How Stelara will be given
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance 'ustekinumab', a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called 'immunosuppressants'. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Moderate to severe Crohn's disease - in adults and children aged 2 years and older
- Moderate to severe ulcerative colitis - in adults

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using

Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before treatment. Make sure you tell your doctor about any illness you have before treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection or if you have any abnormal skin openings (fistulae).**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Stelara is not recommended for use in children under 2 years of age with Crohn's disease or children under 18 years of age with ulcerative colitis because it has not been studied in this age group.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.

- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains sodium
Stelara contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Stelara is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

Stelara contains polysorbate 80
Stelara contains 10.8 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.40 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Stelara will be given

Stelara is intended for use under the guidance and supervision of a doctor experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis.

Stelara 130 mg concentrate for solution for infusion will be given to you by your doctor, through a drip in the vein of your arm (intravenous infusion) over at least one hour. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to receive and for how long.

Adults aged 18 years or older
Crohn's disease or Ulcerative Colitis
- The doctor will work out the recommended intravenous infusion dose for you based on your body weight.

Your body weight	Dose
≤ 55 kg	260 mg
> 55 kg to ≤ 85 kg	390 mg
> 85 kg	520 mg

- After the starting intravenous dose, you will have the next dose of 90 mg Stelara by an injection under your skin ('subcutaneously') 8 weeks later, and then every 12 weeks thereafter.

Children who weigh less than 40 kg
Crohn's disease
- The doctor will work out the recommended intravenous infusion dose for you based on your body surface area (BSA)
- After the starting dose, your doctor will work out the next dose based on your BSA. You will receive this dose of Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin (subcutaneously').

Children who weigh at least 40 kg
Crohn's disease
- The doctor will work out the recommended intravenous infusion dose for you based on your body weight.

Your body weight	Dose
≥ 40 to ≤ 55 kg	260 mg
> 55 kg to ≤ 85 kg	390 mg
> 85 kg	520 mg

- After the starting intravenous dose, you will have the next dose of 90 mg Stelara by an injection under your skin ('subcutaneously') 8 weeks later, and then every 12 weeks thereafter.

How Stelara is given
- The first dose of Stelara for treatment of Crohn's disease or ulcerative colitis is given by a doctor as a drip in the vein of an arm (intravenous infusion).

Talk to your doctor if you have any questions about receiving Stelara.

If you forget to use Stelara
If you forget or miss the appointment for receiving the dose, contact your doctor to reschedule your appointment.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing

    - low blood pressure, which can cause dizziness or light-headedness
    - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

Infusion-related reactions – If you are being treated for Crohn's disease or ulcerative colitis, the first dose of Stelara is given through a drip into a vein (intravenous infusion). Some patients have experienced serious allergic reactions during the infusion.

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea

- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching (‘pruritus’)
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face (‘facial palsy’ or ‘Bell’s palsy’), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Stelara 130 mg concentrate for solution for infusion is given in a hospital or clinic and patients should not need to store or handle it.
- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake the vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Stelara is for single use only. Any diluted infusion solution or unused product remaining in the vial and the syringe should be thrown away in accordance with local requirements.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each vial contains130 mg ustekinumab in 26 mL.
- The other ingredients are EDTA disodium salt dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear, colourless to light yellow concentrate for solution for infusion. It is supplied as a carton pack containing 1 single-dose, glass 30 mL vial. Each vial contains 130 mg ustekinumab in 26 mL of concentrate for solution for infusion.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

България
„Джонсън & Джонсън България" ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Malta
AM MANGION LTD
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Traceability:

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Instructions for dilution:

STELARA concentrate for solution for infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. For adult patients and paediatric patients who weigh at least 40 kg, calculate the dose and the number of STELARA vials needed based on patient weight (see section 4.2, Table 1, Table 3) or for paediatric patients who weigh less than 40 kg, calculate the dose and number of STELARA vials needed based on the patient's body surface area (BSA) (see section 4.2, Table 2). Each 26 mL vial of STELARA contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of STELARA to be added (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials- discard 52 mL, for 3 vials discard 78 mL, for 4 vials- discard 104 mL).
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. For paediatric patients with Crohn's disease weighing less than 40 kg the dose is based on the patient's BSA as a single intravenous (IV) dose of STELARA. Withdraw and then discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 100 mL infusion bag equal to the volume of STELARA to be added. Withdraw the appropriate volume of STELARA from each vial needed and add it to the 100 mL infusion bag. The final volume in the infusion bag should be 100 mL. Gently mix.
5. Visually inspect the diluted solution before infusion. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
6. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
7. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometre).
8. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage
If necessary, the diluted infusion solution may be stored at room temperature. The infusion should be completed within 8 hours of the dilution in the infusion bag. Do not freeze.

Package leaflet: Information for the user

STELARA 45 mg solution for injection
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults and children aged 2 years and older
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.

- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, children with Crohn's disease under 2 years of age or for use in children under 18 years of age with psoriatic arthritis, or ulcerative colitis because it has not been studied in these age groups.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.
- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains polysorbate 80
STELARA contains 0.02 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Stelara is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

Children who weigh less than 40 kg
Crohn's disease
- During treatment, your doctor will work out the recommended intravenous infusion dose for you based on your body surface area (BSA). This will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, your doctor will work out the next dose based on your BSA. You will receive this dose of Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

Children who weigh at least 40 kg
Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will

receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').

In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

How Stelara is given

- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should

If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara

If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara

It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)

- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people):
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary

- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not shake the vials. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.
- If the seal is broken.

Stelara is for single use only. Any unused product remaining in the vial and the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each vial contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution

for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 mL vial. Each vial contains 45 mg ustekinumab in 0.5 mL of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:
Take the vial(s) out of the refrigerator. Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature).

Check the vial(s) to make sure:

- the number of vials and strength is correct
  - If your dose is 45 mg or less, you will get one 45 mg vial of Stelara
  - If your dose is more than 45 mg you will get two 45 mg vials of Stelara and you will need to give yourself two injections. Choose two different sites for these injections (for example one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other. Use a new needle and syringe for each injection.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution in the vial is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution is not discoloured or cloudy and does not contain any foreign particles
- the solution is not frozen.

Children with plaque psoriasis weighing less than 60 kg need a dose lower than 45 mg and children with Crohn's disease weighing less than 40 kg need a dose less than 90 mg. Make sure you know the proper amount (volume) to remove from the vial (s) and type of syringe (s) needed for dosing. If you don't know the amount or type of syringe (s) needed, contact your healthcare provider for further instruction.

Get everything together that you need and lay out on a clean surface. This includes a syringe, needle, antiseptic wipes, a cotton ball or gauze, and a sharps container (see Figure 1).

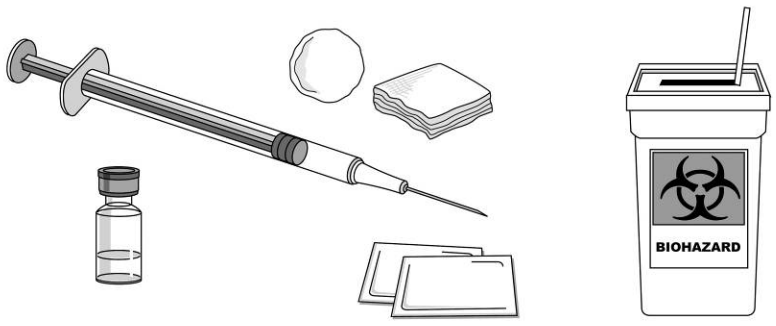
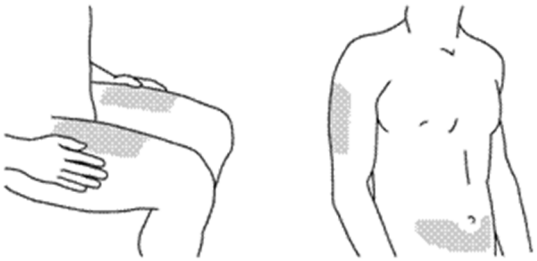


Figure 1

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)

- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site
- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection

3. Prepare the dose:
- Take the cap off the top of the vial (see Figure 3)



Figure 3

- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.
- Pick up the syringe and remove the needle cover
- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid prescribed by your doctor
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe (see Figure 4)

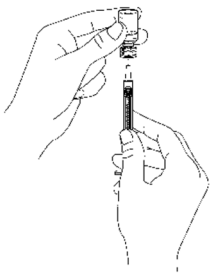


Figure 4

- Remove the needle from the vial
- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe (see Figure 5)

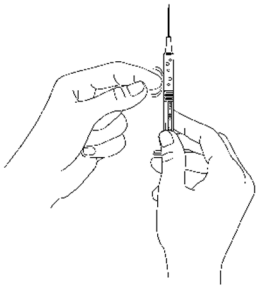


Figure 5

- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:
- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin

5. After the injection:
- There may be a small amount of blood or liquid at the injection site. This is normal
- Press a cotton ball or gauze over the injection site and hold for 10 seconds
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:
- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Never re-use needles and syringes, for your safety and health, and for the safety of others. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed of in your garbage.

Package leaflet: Information for the user

STELARA 45 mg solution for injection in pre-filled syringe
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults and children aged 2 years and older
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using

these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, children with Crohn's disease under 2 years of age or for use in children under 18 years of age with psoriatic arthritis, or ulcerative colitis because it has not been studied in these age groups.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.
- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains polysorbate 80
Stelara contains 0.02 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Stelara is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

Children who weigh less than 40 kg
Crohn's disease
- During treatment, your doctor will work out the recommended intravenous infusion dose for you based on your body surface area (BSA). This will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, your doctor will work out the next dose based on your BSA. You will receive this dose of Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

Children who weigh at least 40 kg
Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression

- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- If needed, individual Stelara pre-filled syringes may also be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a syringe has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 45 mg ustekinumab in 0.5 mL of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

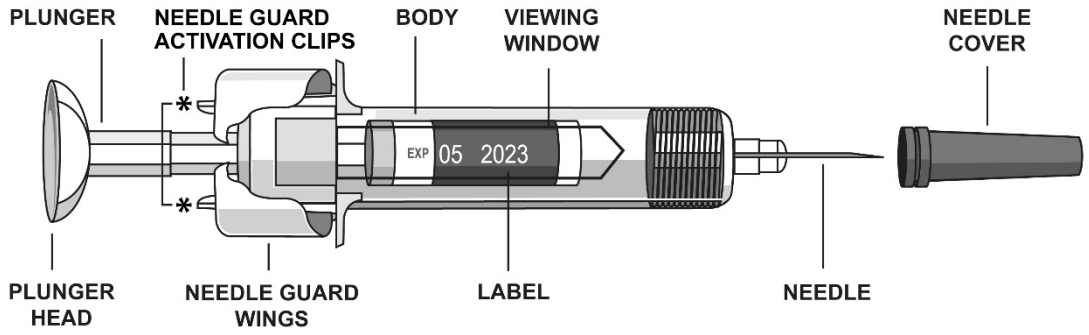


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:

Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so
- Do not touch the needle guard activation clips (as indicated by asterisks * in Figure 1) to prevent prematurely covering the needle with the needle guard.

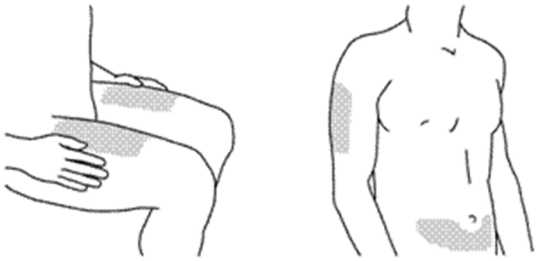
Check the pre-filled syringe(s) to make sure

- the number of pre-filled syringes and strength is correct
  - If your dose is 45 mg you will get one 45 mg pre-filled syringe of Stelara
  - If your dose is 90 mg you will get two 45 mg pre-filled syringes of Stelara and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection

3. Remove the needle cover (see Figure 3):

- The needle cover should not be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

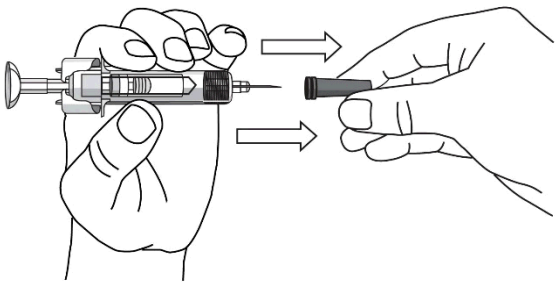


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:

- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)

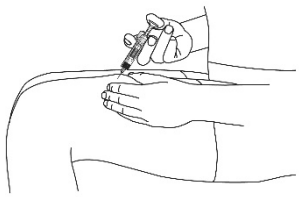


Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

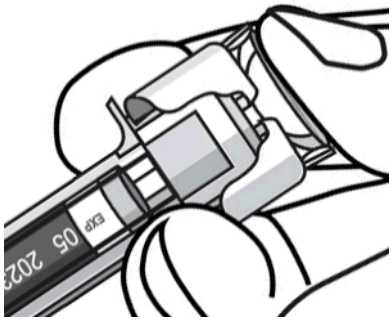


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

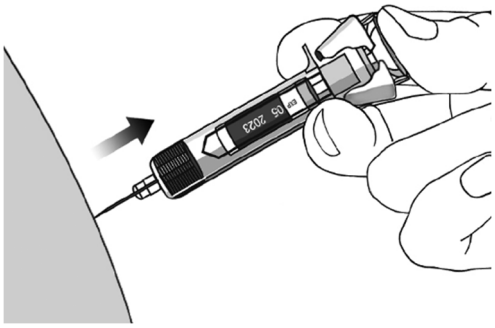


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

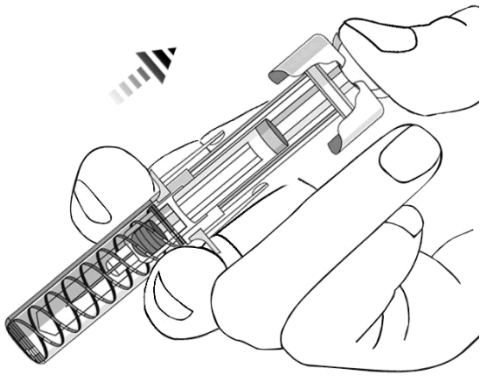


Figure 7

5. After the injection:

- There may be a small amount of blood or liquid at the injection site. This is normal.
- Press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.

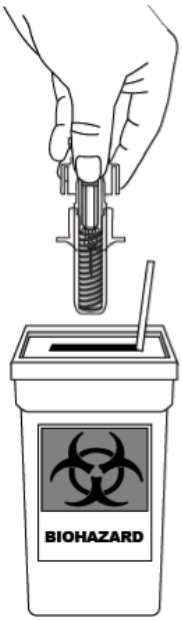


Figure 8

Package leaflet: Information for the user

STELARA 90 mg solution for injection in pre-filled syringe
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Stelara to a child, please read this information carefully.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance ‘ustekinumab’, a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called ‘immunosuppressants’. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults and children aged 6 years and older
- Psoriatic arthritis - in adults
- Moderate to severe Crohn’s disease - in adults and children aged 2 years and older
- Moderate to severe ulcerative colitis – in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Stelara is used in children and adolescents aged 6 years and older with moderate to severe plaque psoriasis who are unable to tolerate phototherapy or other systemic therapies or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using

these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
Stelara is not recommended for use in children with psoriasis under 6 years of age, children with Crohn's disease under 2 years of age or for use in children under 18 years of age with psoriatic arthritis, or ulcerative colitis because it has not been studied in these age groups.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.
- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara -do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains polysorbate 80
Stelara contains 0.04 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Stelara is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

Children and adolescents aged 6 years or older
Psoriasis
- The doctor will work out the right dose for you, including the amount (volume) of Stelara to be injected to give the right dose. The right dose for you will depend on your body weight at the time each dose is given.
- A 45 mg vial is available for children who need to receive less than the full 45 mg dose.
- If you weigh less than 60 kg, the recommended dose is 0.75 mg of Stelara per kg body weight.
- If you weigh 60 kg to 100 kg, the recommended dose is 45 mg Stelara.
- If you weigh more than 100 kg, the recommended dose is 90 mg Stelara.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks.

Children who weigh less than 40 kg
Crohn's disease
- During treatment, your doctor will work out the recommended intravenous infusion for you based on your body surface area (BSA). This will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, your doctor will work out the next dose based on your BSA. You will receive this dose of Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

Children who weigh at least 40 kg
Crohn's disease
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').

In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks or every 4 weeks. Your doctor will decide when you should receive your next dose.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, skin infections, shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**

- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**

- Tooth infections
- Vaginal yeast infection
- Depression

- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- If needed, individual Stelara pre-filled syringes may also be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from light. Record the date when the pre-filled syringe is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a syringe has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the pre-filled syringes. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the syringe should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled syringe. Each pre-filled syringe contains 90 mg ustekinumab in 1 mL of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for administration

At the start of treatment, your healthcare provider will assist you with your first injection. However, you and your doctor may decide that you may inject Stelara yourself. If this happens, you will get training on how to inject Stelara. Talk to your doctor if you have any questions about giving yourself an injection.

- Do not mix Stelara with other liquids for injection
- Do not shake Stelara pre-filled syringes. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

Figure 1 shows what the pre-filled syringe looks like.

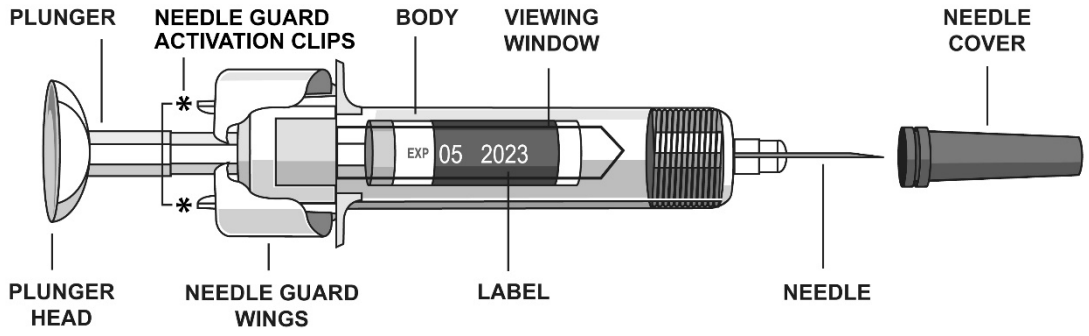


Figure 1

1. Check the number of pre-filled syringes and prepare the materials:

Preparing for use of the pre-filled syringe

- Take the pre-filled syringe(s) out of the refrigerator. Let the pre-filled syringe stand outside the box for about half an hour. This will let the liquid come to a comfortable temperature for injection (room temperature). Do not remove the syringe's needle cover while allowing it to reach room temperature
- Hold the pre-filled syringe by the body of the syringe with the covered needle pointing upward
- Do not hold by the plunger head, plunger, needle guard wings, or needle cover
- Do not pull back on the plunger at any time
- Do not remove the needle cover from the pre-filled syringe until instructed to do so
- Do not touch the needle guard activation clips (as indicated by asterisks * in Figure 1) to prevent prematurely covering the needle with the needle guard.

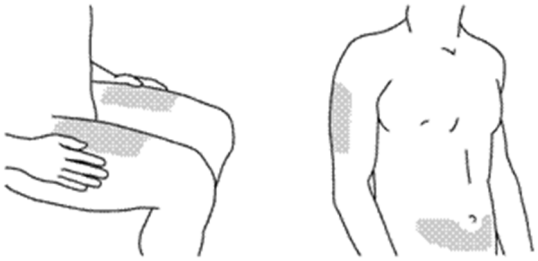
Check the pre-filled syringe(s) to make sure

- the number of pre-filled syringes and strength is correct
  - If your dose is 90 mg you will get one 90 mg pre-filled syringe of Stelara.
- it is the right medicine
- it has not passed its expiry date
- the pre-filled syringe is not damaged
- the solution in the pre-filled syringe is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow
- the solution in the pre-filled syringe is not discoloured or cloudy and does not contain any foreign particles
- the solution in the pre-filled syringe is not frozen.

Get everything together that you need and lay out on a clean surface. This includes antiseptic wipes, a cotton ball or gauze, and a sharps container.

2. Choose and prepare the injection site:
Choose an injection site (see Figure 2)

- Stelara is given by injection under the skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms as an injection site.



*Areas in gray are recommended injection sites.

Figure 2

Prepare the injection site

- Wash your hands very well with soap and warm water
- Wipe the injection site on the skin with an antiseptic wipe
- Do not touch this area again before giving the injection.

3. Remove the needle cover (see Figure 3):

- The needle cover should not be removed until you are ready to inject the dose
- Pick up the pre-filled syringe, hold the body of the syringe with one hand
- Pull the needle cover straight off and throw it away. Do not touch the plunger while you do this

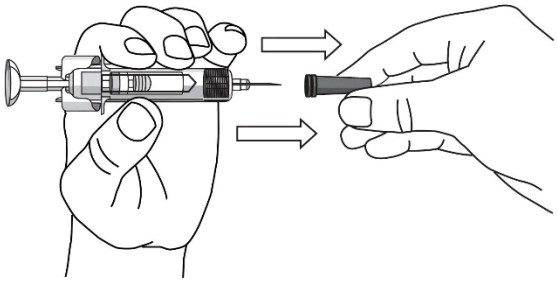


Figure 3

- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed
- Do not touch the needle or allow it to touch any surface
- Do not use the pre-filled syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist
- Inject the dose promptly after removing the needle cover.

4. Inject the dose:

- Hold the pre-filled syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Do not pull back on the plunger at any time
- In a single and swift motion, insert the needle through the skin as far as it will go (see Figure 4)

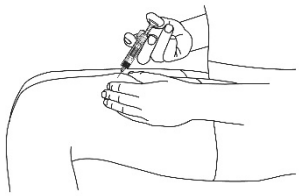


Figure 4

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see Figure 5)

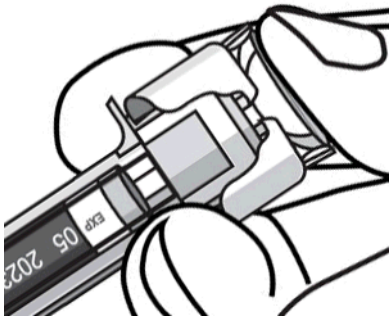


Figure 5

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see Figure 6)

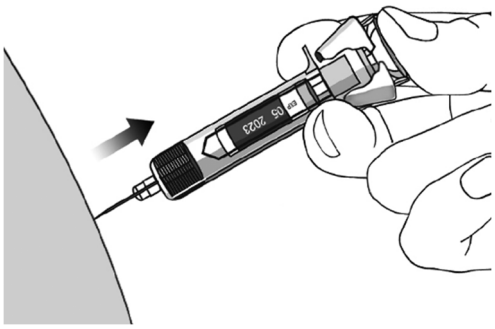


Figure 6

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by Figure 7:

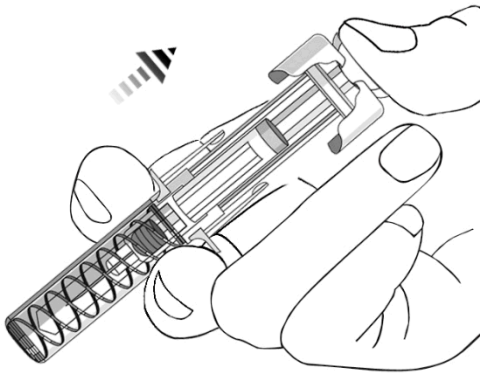


Figure 7

5. After the injection:

- There may be a small amount of blood or liquid at the injection site. This is normal.
- Press a cotton ball or gauze over the injection site and hold for 10 seconds.
- Do not rub the skin at the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

6. Disposal:

- Used syringes should be placed in a puncture-resistant container, like a sharps container (see Figure 8). Never re-use a syringe, for your safety and health and for the safety of others. Dispose of your sharps container according to your local regulations
- Antiseptic wipes and other supplies can be disposed of in your garbage.

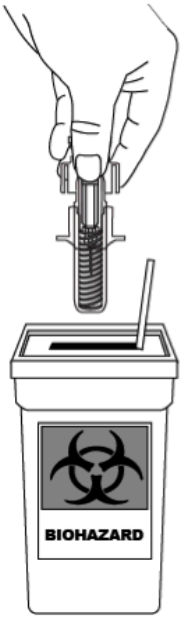


Figure 8

Package leaflet: Information for the user

STELARA 45 mg solution for injection in pre-filled pen
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance 'ustekinumab', a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called 'immunosuppressants'. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara administered using the pre-filled pen is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults
- Psoriatic arthritis - in adults
- Moderate to severe Crohn's disease - in adults
- Moderate to severe ulcerative colitis - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara administered using the pre-filled pen is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
The Stelara pre-filled pen is not recommended for use in children and adolescents under 18 years of age with psoriasis or Crohn's disease because it has not been studied in this age group. The pre-filled syringe or vial should be used instead for children 6 years of age and older and adolescents with psoriasis. The solution for infusion, pre-filled vial or syringe should be used instead for children 2 years of age and older with Crohn's disease.

Stelara is not recommended for use in children and adolescents under 18 years of age with psoriatic arthritis, or ulcerative colitis or children with Crohn's disease under 2 years of age because it has not been studied in these age groups.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.
- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara - do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains polysorbate 80
Stelara contains 0.02 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Stelara is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.

- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.

- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:

- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin

conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)**:**
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)**:**
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled pen in the outer carton in order to protect from light.

- If needed, individual Stelara pre-filled pens may also be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from light. Record the date when the pre-filled pen is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a pre-filled pen has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the pre-filled pen if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the pre-filled pens. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the pre-filled pen should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled pen. Each pre-filled pen contains 45 mg ustekinumab in 0.5 mL of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

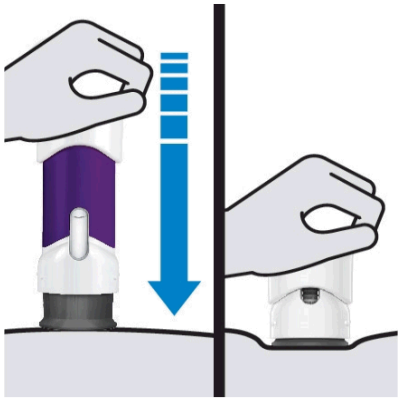
Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Stelara
(ustekinumab)
injection, for subcutaneous use
Pre-filled pen



This “Instructions for Use” contains information on how to inject Stelara.

Important
Stelara comes in a single-dose pre-filled pen containing one 45 mg dose or one 90 mg dose.

During injection, push handle all the way down until purple body is not visible to inject the full dose. DO NOT LIFT PRE-FILLED PEN during injection! If you do, the pre-filled pen will lock and you will not get the full dose.

If your doctor decides that you or a caregiver may be able to give your injections of Stelara at home, you should receive training on the right way to prepare and inject Stelara using the pre-filled pen. **Do not try to inject yourself until you have been trained by your doctor.**

Each pre-filled pen can only be used one time. Throw it away (see Step 3) after use even if there is medicine left in it.

Do not reuse the pre-filled pen.

Read these Instructions for Use before using the Stelara pre-filled pen and each time you get a new pre-filled pen. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

If you cannot give yourself the injection:
- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

To reduce the risk of accidental needle sticks, each pre-filled pen has a needle guard that automatically covers the needle and locks after you have given your injection and the injector is lifted. Do not lift the pre-filled pen during the injection until the injection is complete.

The needle cover inside the bottom cap of the pre-filled pen contains latex. **Do not handle the needle cover if you are allergic to latex.**
Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.



Storage information

Store in refrigerator at 2° to 8°C. If needed, store at room temperature up to 30°C for up to 30 days in the original carton. **Do not return to refrigerator** once stored at room temperature.

Do not freeze the pre-filled pen.

Keep the pre-filled pen and all medicines out of reach of children.

Do not shake the pre-filled pen. Shaking may damage the Stelara medicine. If the pre-filled pen has been shaken, do not use it. Get a new pre-filled pen.

Keep the pre-filled pen in the original carton to protect from light and physical damage.



Need help?

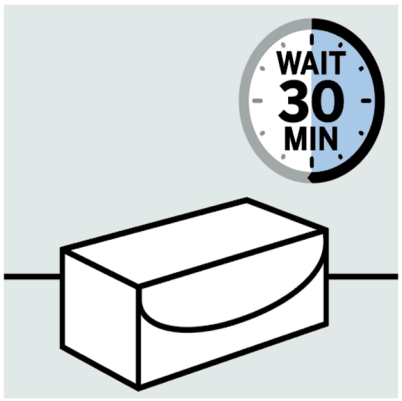
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.



Gather the following supplies.
Provided in the carton:
- **Pre-filled pen injector**

Not provided in the carton:
- **Alcohol swabs**
- **Cotton balls or gauze pads**
- **Adhesive bandages**
- **Sharps container** (See Step 3)

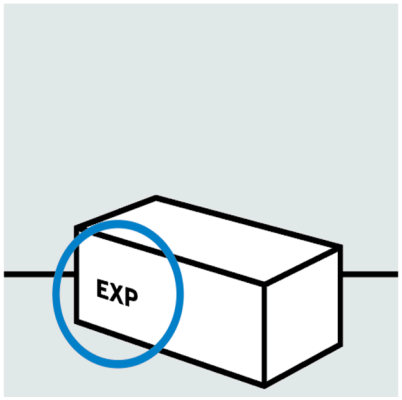
1. Preparing to Inject Stelara



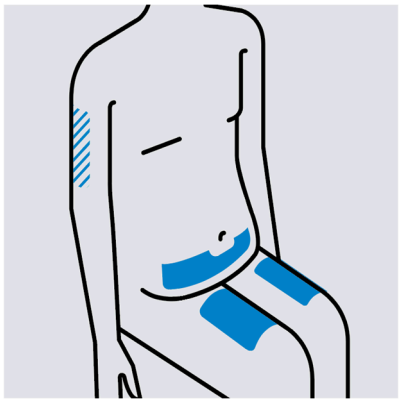
Gather carton(s)
If refrigerated, remove the pre-filled pen carton(s) from the refrigerator and place on a flat surface. Leave at **room temperature for at least 30 minutes** before use.
Do not warm any other way.

If your dose is 45 mg, you will receive one 45 mg pre-filled pen.
If your dose is 90 mg, you will receive one 90 mg or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens, follow Steps 1-3 for both injections.

Choose a different injection site for the second injection.



Check the expiry date ('EXP') and seals on the carton(s)
Do not use the pre-filled pen if the seals on the carton are broken or if the expiry date has passed.
Do not use the pre-filled pen if it has been kept at room temperature for longer than 30 days or if it has been stored above 30°C. Call your doctor or pharmacist for a new pre-filled pen.

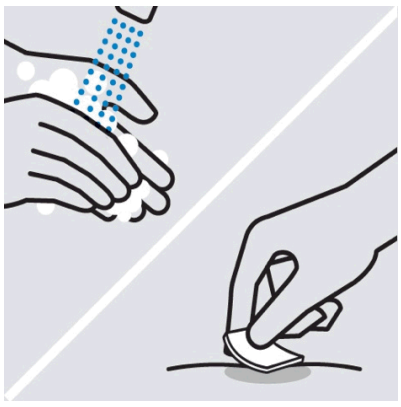


Choose injection site
Select from the following areas for your injection:
- Front of thighs
- Lower stomach area (lower abdomen), except for a 5-centimetre area right around your navel (belly-button)

If someone else is giving you the injection, they may also use:
- Back of upper arms

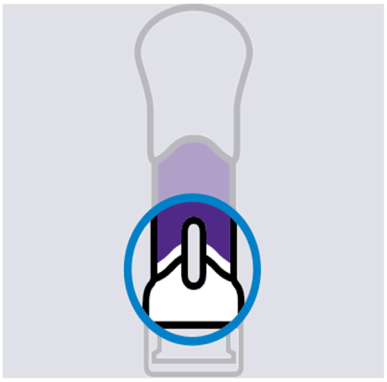
Do not inject into skin that is tender, bruised, red, or hard.

Use a different injection site for each injection.



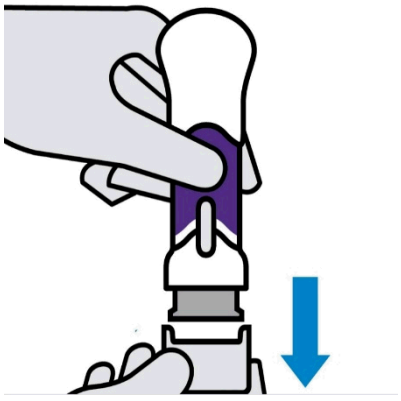
Wash hands
Wash your hands well with soap and warm water.

Clean injection site
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

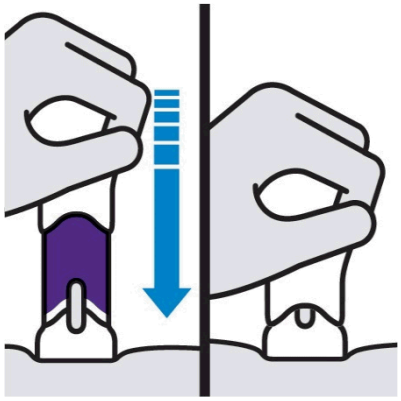


Inspect liquid in window
Choose a well-lit, clean, flat work surface.
Take the pre-filled pen out of the carton and check for damage.
Check the liquid in the viewing window. It should be **clear to slightly opalescent** and **colourless to light yellow** and may contain **tiny white or clear particles** and **one or more air bubbles**. This is normal.
Do not inject if the liquid is frozen, cloudy, discoloured, or has large particles. Call your doctor or pharmacist for a new pre-filled pen.

2. Injecting Stelara



Pull off bottom cap
Keep hands away from the needle guard after the cap is removed. It is normal to see a few drops of liquid.
Inject Stelara within 5 minutes of removing the cap.
Do not put the cap back on. This could damage the needle.
Do not use a pre-filled pen if it is dropped after removing the cap. Call your doctor or pharmacist for a new pre-filled pen.



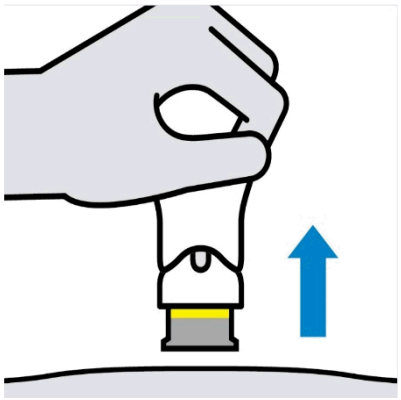
Place straight on skin. Push handle all the way down until purple body is not visible.

DO NOT LIFT PRE-FILLED PEN during injection!
If you do, the needle guard will lock, showing a yellow band, and you will not get the full dose.

You may hear a click when the injection begins. Keep pushing.
If you feel resistance, keep pushing. This is normal.
The medication injects as you push. Do this at a speed that is comfortable for you.



Confirm your injection is complete
Your injection is complete when:
- The purple body is not visible.
- You cannot press the handle down anymore.
- You may hear a click.

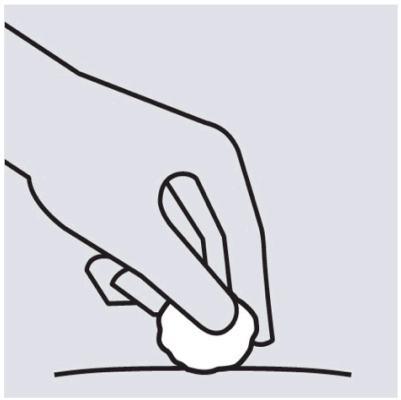


Lift straight up
The yellow band indicates that the needle guard is locked into place.

3. After your injection



Dispose of the pre-filled pen
Put the used pre-filled pen in a sharps disposal container right away after use.
Do not throw away (dispose of) the pre-filled pens in the household trash.
Do not recycle your used sharps disposal container.



Check injection site
There may be a small amount of blood or liquid at the injection site. This is normal. Press a cotton ball or gauze pad to the injection site until any bleeding stops.
Do not rub the injection site.
If needed, cover the injection site with a bandage.

If you receive two 45 mg pre-filled pens for a 90 mg dose, repeat Steps 1-3 with the second pre-filled pen. **Choose a different injection site for the second injection.**

Package leaflet: Information for the user

STELARA 90 mg solution for injection in pre-filled pen
ustekinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

This leaflet has been written for the person taking the medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Stelara is and what it is used for
2. What you need to know before you use Stelara
3. How to use Stelara
4. Possible side effects
5. How to store Stelara
6. Contents of the pack and other information

1. What Stelara is and what it is used for

What Stelara is
Stelara contains the active substance 'ustekinumab', a monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind specifically to certain proteins in the body.

Stelara belongs to a group of medicines called 'immunosuppressants'. These medicines work by weakening part of the immune system.

What Stelara is used for
Stelara administered using the pre-filled pen is used to treat the following inflammatory diseases:
- Plaque psoriasis - in adults
- Psoriatic arthritis - in adults
- Moderate to severe Crohn's disease - in adults
- Moderate to severe ulcerative colitis - in adults

Plaque psoriasis
Plaque psoriasis is a skin condition that causes inflammation affecting the skin and nails. Stelara will reduce the inflammation and other signs of the disease.

Stelara administered using the pre-filled pen is used in adults with moderate to severe plaque psoriasis, who cannot use ciclosporin, methotrexate or phototherapy, or where these treatments did not work.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Stelara to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.
- Slow down the damage to your joints.

Crohn's disease
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or are intolerant to these medicines, you may be given Stelara to reduce the signs and symptoms of your disease.

2. What you need to know before you use Stelara

Do not use Stelara
- **If you are allergic to ustekinumab** or any of the other ingredients of this medicine (listed in section 6).
- **If you have an active infection** which your doctor thinks is important.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Warnings and precautions
Talk to your doctor or pharmacist before using Stelara. Your doctor will check how well you are before each treatment. Make sure you tell your doctor about any illness you have before each treatment. Also tell your doctor if you have recently been near anyone who might have tuberculosis. Your doctor will examine you and do a test for tuberculosis, before you have Stelara. If your doctor thinks you are at risk of tuberculosis, you may be given medicines to treat it.

Look out for serious side effects
Stelara can cause serious side effects, including allergic reactions and infections. You must look out for certain signs of illness while you are taking Stelara. See 'Serious side effects' in section 4 for a full list of these side effects.

Before you use Stelara tell your doctor:
- **If you ever had an allergic reaction to Stelara.** Ask your doctor if you are not sure.
- **If you have ever had any type of cancer** – this is because immunosuppressants like Stelara weaken part of the immune system. This may increase the risk of cancer.
- **If you have been treated for psoriasis with other biologic medicines (a medicine produced from a biological source and usually given by injection)** – the risk of cancer may be higher.
- **If you have or have had a recent infection.**
- **If you have any new or changing lesions** within psoriasis areas or on normal skin.
- **If you have ever had an allergic reaction to latex or Stelara injection** – the container of this medicinal product contains latex rubber, which may cause severe allergic reactions in people who are sensitive to latex. See 'Look out for serious side effects' in section 4 for the signs of an allergic reaction.
- **If you are having any other treatment for psoriasis and/or psoriatic arthritis** – such as another immunosuppressant or phototherapy (when your body is treated with a type of ultraviolet (UV) light). These treatments may also weaken part of the immune system. Using these therapies together with Stelara has not been studied. However it is possible it may increase the chance of diseases related to a weaker immune system.
- **If you are having or have ever had injections to treat allergies** – it is not known if Stelara may affect these.
- **If you are 65 years of age or over** – you may be more likely to get infections.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Stelara.

Some patients have experienced lupus-like reactions including skin lupus or lupus-like syndrome during treatment with ustekinumab. Talk to your doctor right away if you experience a red, raised, scaly rash sometimes with a darker border, in areas of the skin that are exposed to the sun or with joint pains.

Heart attack and strokes
Heart attack and strokes have been observed in a study in patients with psoriasis treated with Stelara. Your doctor will regularly check your risk factors for heart disease and stroke in order to ensure that they are appropriately treated. Seek medical attention right away if you develop chest pain, weakness or abnormal sensation on one side of your body, facial droop, or speech or visual abnormalities.

Children and adolescents
The Stelara pre-filled pen is not recommended for use in children and adolescents under 18 years of age with psoriasis or Crohn's disease because it has not been studied in this age group. The pre-filled syringe or vial should be used instead for children 6 years of age and older and adolescents with psoriasis. The solution for infusion, pre-filled vial or syringe should be used instead for children 2 years of age and older with Crohn's disease.

Stelara is not recommended for use in children and adolescents under 18 years of age with psoriatic arthritis, ulcerative colitis or children with Crohn's disease under 2 years of age because it has not been studied in these age groups.

Other medicines, vaccines and Stelara
Tell your doctor or pharmacist:
- If you are taking, have recently taken or might take any other medicines.
- If you have recently had or are going to have a vaccination. Some types of vaccines (live vaccines) should not be given while using Stelara.
- If you received Stelara while pregnant, tell your baby's doctor about your Stelara treatment before the baby receives any vaccine, including live vaccines, such as the BCG vaccine (used to prevent tuberculosis). Live vaccines are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.

Pregnancy and breast-feeding
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- A higher risk of birth defects has not been seen in babies exposed to Stelara in the womb. However, there is limited experience with Stelara in pregnant women. It is therefore preferable to avoid the use of Stelara in pregnancy.
- If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Stelara and for at least 15 weeks after the last Stelara treatment.
- Stelara can pass across the placenta to the unborn baby. If you received Stelara during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals if you received Stelara during your pregnancy before the baby receives any vaccine. Live vaccines such as the BCG vaccine (used to prevent tuberculosis) are not recommended for your baby in the first twelve months after birth if you received Stelara during the pregnancy unless your baby's doctor recommends otherwise.
- Ustekinumab may pass into breast milk in very small amounts. Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you should breast-feed or use Stelara -do not do both.

Driving and using machines
Stelara has no or negligible influence on the ability to drive and use machines.

Stelara contains polysorbate 80
Stelara contains 0.04 mg of polysorbate 80 (E433) in each dosage unit which is equivalent to 0.04 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Stelara

Stelara is intended for use under the guidance and supervision of a doctor experienced in treating conditions for which Stelara is intended.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Talk to your doctor about when you will have your injections and follow-up appointments.

How much Stelara is given
Your doctor will decide how much Stelara you need to use and for how long.

Adults aged 18 years or older
Psoriasis or Psoriatic Arthritis
- The recommended starting dose is 45 mg Stelara. Patients who weigh more than 100 kilograms (kg) may start on a dose of 90 mg instead of 45 mg.
- After the starting dose, you will have the next dose 4 weeks later, and then every 12 weeks. The following doses are usually the same as the starting dose.

Crohn's disease or Ulcerative Colitis
- During treatment, the first dose of approximately 6 mg/kg Stelara will be given by your doctor through a drip in a vein in your arm (intravenous infusion). After the starting dose, you will receive the next dose of 90 mg Stelara after 8 weeks, then every 12 weeks thereafter by an injection under the skin ('subcutaneously').
- In some patients, after the first injection under the skin, 90 mg Stelara may be given every 8 weeks. Your doctor will decide when you should receive your next dose.

How Stelara is given
- Stelara is given as an injection under the skin ('subcutaneously'). At the start of your treatment, medical or nursing staff may inject Stelara.
- However, you and your doctor may decide that you may inject Stelara yourself. In this case you will get training on how to inject Stelara yourself.
- For instructions on how to inject Stelara, see 'Instructions for administration' at the end of this leaflet.

Talk to your doctor if you have any questions about giving yourself an injection.

If you use more Stelara than you should
If you have used or been given too much Stelara, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use Stelara
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using Stelara
It is not dangerous to stop using Stelara. However, if you stop, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Some patients may have serious side effects that may need urgent treatment.

Allergic reactions – these may need urgent treatment. Tell your doctor or get emergency medical help straight away if you notice any of the following signs.
- Serious allergic reactions ('anaphylaxis') are rare in people taking Stelara (may affect up to 1 in 1,000 people). Signs include:
  - difficulty breathing or swallowing
  - low blood pressure, which can cause dizziness or light-headedness
  - swelling of the face, lips, mouth or throat.
- Common signs of an allergic reaction include skin rash and hives (these may affect up to 1 in 100 people).

In rare cases, allergic lung reactions and lung inflammation have been reported in patients who receive ustekinumab. Tell your doctor right away if you develop symptoms such as cough, shortness of breath, and fever.

If you have a serious allergic reaction, your doctor may decide that you should not use Stelara again.

Infections – these may need urgent treatment. Tell your doctor straight away if you notice any of the following signs.
- Infections of the nose or throat and common cold are common (may affect up to 1 in 10 people)
- Infections of the chest are uncommon (may affect up to 1 in 100 people)
- Inflammation of tissue under the skin ('cellulitis') is uncommon (may affect up to 1 in 100 people)
- Shingles (a type of painful rash with blisters) are uncommon (may affect up to 1 in 100 people)

Stelara may make you less able to fight infections. Some infections could become serious and may include infections caused by viruses, fungi, bacteria (including tuberculosis), or parasites, including infections that mainly occur in people with a weakened immune system (opportunistic infections). Opportunistic infections of the brain (encephalitis, meningitis), lungs, and eye have been reported in patients receiving treatment with ustekinumab.

You must look out for signs of infection while you are using Stelara. These include:
- fever, flu-like symptoms, night sweats, weight loss
- feeling tired or short of breath; cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters
- burning when passing water
- diarrhoea
- visual disturbance or vision loss
- headache, neck stiffness, light sensitivity, nausea or confusion.

Tell your doctor straight away if you notice any of these signs of infection. These may be signs of infections such as chest infections, or skin infections or shingles or opportunistic infections that could have serious complications. Tell your doctor if you have any kind of infection that will not go away or keeps coming back. Your doctor may decide that you should not use Stelara until the infection goes away. Also tell your doctor if you have any open cuts or sores as they might get infected.

Shedding of skin – increase in redness and shedding of skin over a larger area of the body may be symptoms of erythrodermic psoriasis or exfoliative dermatitis, which are serious skin conditions. You should tell your doctor straight away if you notice any of these signs.

Other side effects

Common side effects (may affect up to 1 in 10 people)**:**
- Diarrhoea
- Nausea
- Vomiting
- Feeling tired
- Feeling dizzy
- Headache
- Itching ('pruritus')
- Back, muscle or joint pain
- Sore throat
- Redness and pain where the injection is given
- Sinus infection

Uncommon side effects (may affect up to 1 in 100 people)**:**
- Tooth infections
- Vaginal yeast infection
- Depression
- Blocked or stuffy nose
- Bleeding, bruising, hardness, swelling and itching where the injection is given
- Feeling weak
- Drooping eyelid and sagging muscles on one side of the face ('facial palsy' or 'Bell's palsy'), which is usually temporary
- A change in psoriasis with redness and new tiny, yellow or white skin blisters, sometimes accompanied by fever (pustular psoriasis)
- Peeling of the skin (skin exfoliation)
- Acne

Rare side effects (may affect up to 1 in 1,000 people)**:**
- Redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis). Similar symptoms sometimes develop as a natural change in the type of psoriasis symptoms (erythrodermic psoriasis)
- Inflammation of small blood vessels, which can lead to a skin rash with small red or purple bumps, fever or joint pain (vasculitis)

Very rare side effects (may affect up to 1 in 10,000 people)**:**
- Blistering of the skin that may be red, itchy, and painful (Bullous pemphigoid).
- Skin lupus or lupus-like syndrome (red, raised scaly rash on areas of the skin exposed to the sun possibly with joint pains).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Stelara

- Keep this medicine out of the sight and reach of children.
- Store in a refrigerator (2°C–8°C). Do not freeze.
- Keep the pre-filled pen in the outer carton in order to protect from light.
- If needed, individual Stelara pre-filled pens may also be stored at room temperature up to 30°C for a maximum single period of up to 30 days in the original carton in order to protect from

light. Record the date when the pre-filled pen is first removed from the refrigerator and the discard date in the space provided on the outer carton. The discard date must not exceed the original expiry date printed on the carton. Once a pre-filled pen has been stored at room temperature (up to 30°C), it should not be returned to the refrigerator. Discard the pre-filled pen if not used within 30 days at room temperature storage or by the original expiry date, whichever is earlier.
- Do not shake the pre-filled pen. Prolonged vigorous shaking may damage the medicine.

Do not use this medicine:
- After the expiry date which is stated on the label and the carton after 'EXP'. The expiry date refers to the last day of that month.
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see section 6 'What Stelara looks like and contents of the pack').
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated).
- If the product has been shaken vigorously.

Stelara is for single use only. Any unused product remaining in the pre-filled pen should be thrown away. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Stelara contains
- The active substance is ustekinumab. Each pre-filled pen contains 90 mg ustekinumab in 1 mL.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections.

What Stelara looks like and contents of the pack
Stelara is a clear to slightly opalescent (having a pearl-like shine), colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 1 mL pre-filled pen. Each pre-filled pen contains 90 mg ustekinumab in 1 mL of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: 0800 93 377
info_belux@its.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
medinfo-de@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor ehf.
Sími: +354 535 7000
janssen@vistor.is

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: 800 29 504
info_belux@its.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: 0800 242 42 42
info_nl@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
JNJ-SI-safety@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle
Latvijā
Tel: +371 678 93561
lv@its.jnj.com

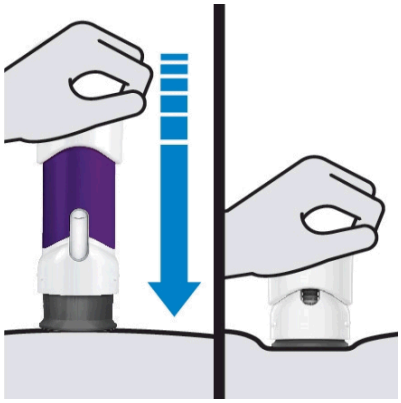
Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Stelara
(ustekinumab)
injection, for subcutaneous use
Pre-filled pen



This “Instructions for Use” contains information on how to inject Stelara.

Important
Stelara comes in a single-dose pre-filled pen containing one 45 mg dose or one 90 mg dose.

During injection, push handle all the way down until purple body is not visible to inject the full dose. DO NOT LIFT PRE-FILLED PEN during injection! If you do, the pre-filled pen will lock and you will not get the full dose.

If your doctor decides that you or a caregiver may be able to give your injections of Stelara at home, you should receive training on the right way to prepare and inject Stelara using the pre-filled pen. **Do not try to inject yourself until you have been trained by your doctor.**

Each pre-filled pen can only be used one time. Throw it away (see Step 3) after use even if there is medicine left in it.

Do not reuse the pre-filled pen.

Read these Instructions for Use before using the Stelara pre-filled pen and each time you get a new pre-filled pen. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

If you cannot give yourself the injection:
- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

To reduce the risk of accidental needle sticks, each pre-filled pen has a needle guard that automatically covers the needle and locks after you have given your injection and the injector is lifted. Do not lift the pre-filled pen during the injection until the injection is complete.

The needle cover inside the bottom cap of the pre-filled pen contains latex. **Do not handle the needle cover if you are allergic to latex.**
Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.

Storage information
Store in refrigerator at 2° to 8°C. If needed, store at room temperature up to 30°C for up to 30 days in

the original carton. **Do not return to refrigerator** once stored at room temperature.

Do not freeze the pre-filled pen.

Keep the pre-filled pen and all medicines out of reach of children.

Do not shake the pre-filled pen. Shaking may damage the Stelara medicine. If the pre-filled pen has been shaken, do not use it. Get a new pre-filled pen.

Keep the pre-filled pen in the original carton to protect from light and physical damage.



Need help?

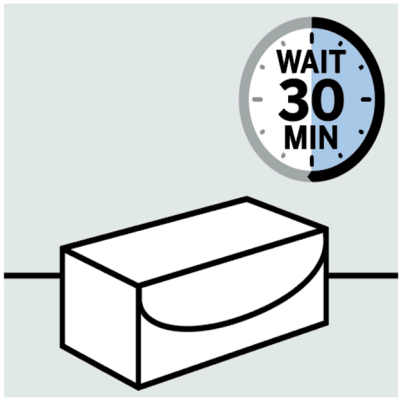
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.



Gather the following supplies.
Provided in the carton:
- **Pre-filled pen injector**

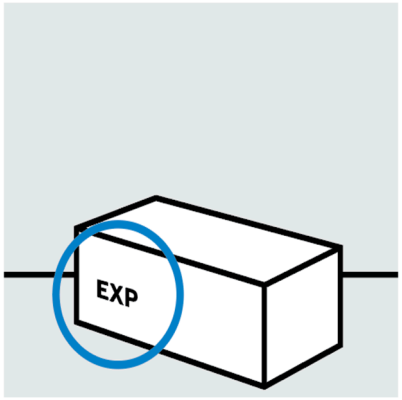
Not provided in the carton:
- **Alcohol swabs**
- **Cotton balls or gauze pads**
- **Adhesive bandages**
- **Sharps container** (See Step 3)

1. Preparing to Inject Stelara

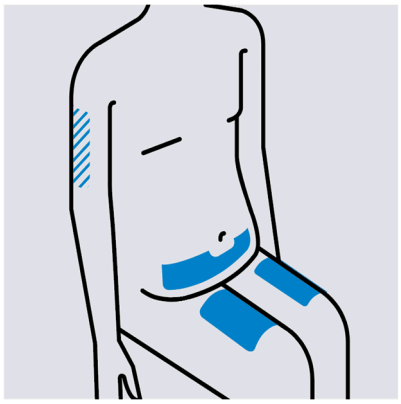


Gather carton(s)
If refrigerated, remove the pre-filled pen carton(s) from the refrigerator and place on a flat surface. Leave at **room temperature for at least 30 minutes** before use.
Do not warm any other way.

If your dose is 45 mg, you will receive one 45 mg pre-filled pen.
If your dose is 90 mg, you will receive one 90 mg or two 45 mg pre-filled pens. If you receive two 45 mg pre-filled pens, follow Steps 1-3 for both injections.
Choose a different injection site for the second injection.



Check the expiry date ('EXP') and seals on the carton(s)
Do not use the pre-filled pen if the seals on the carton are broken or if the expiry date has passed.
Do not use the pre-filled pen if it has been kept at room temperature for longer than 30 days or if it has been stored above 30°C. Call your doctor or pharmacist for a new pre-filled pen.

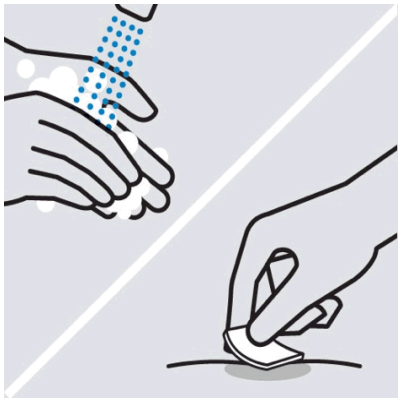


Choose injection site
Select from the following areas for your injection:
- Front of thighs
- Lower stomach area (lower abdomen), except for a 5-centimetre area right around your navel (belly-button)

If someone else is giving you the injection, they may also use:
- Back of upper arms

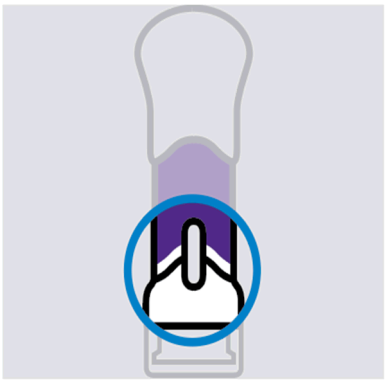
Do not inject into skin that is tender, bruised, red, or hard.

Use a different injection site for each injection.



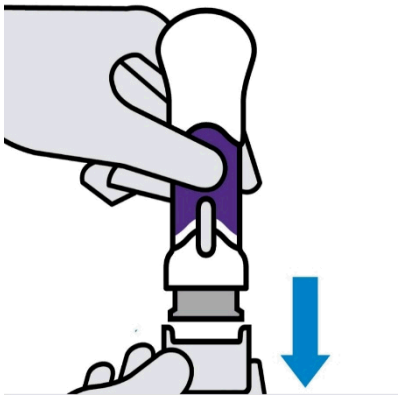
Wash hands
Wash your hands well with soap and warm water.

Clean injection site
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

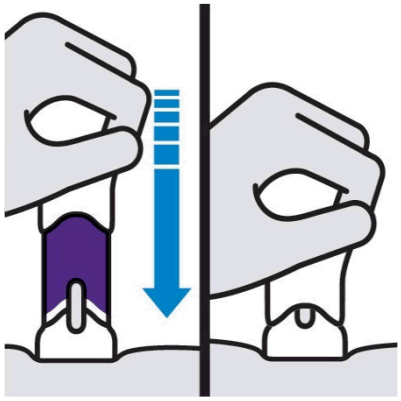


Inspect liquid in window
Choose a well-lit, clean, flat work surface.
Take the pre-filled pen out of the carton and check for damage.
Check the liquid in the viewing window. It should be **clear to slightly opalescent** and **colourless to light yellow** and may contain **tiny white or clear particles** and **one or more air bubbles**. This is normal.
Do not inject if the liquid is frozen, cloudy, discoloured, or has large particles. Call your doctor or pharmacist for a new pre-filled pen.

2. Injecting Stelara



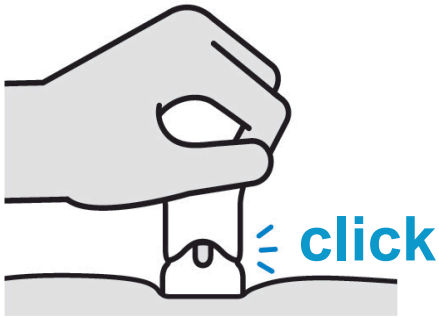
Pull off bottom cap
Keep hands away from the needle guard after the cap is removed. It is normal to see a few drops of liquid.
Inject Stelara within 5 minutes of removing the cap.
Do not put the cap back on. This could damage the needle.
Do not use a pre-filled pen if it is dropped after removing the cap. Call your doctor or pharmacist for a new pre-filled pen.



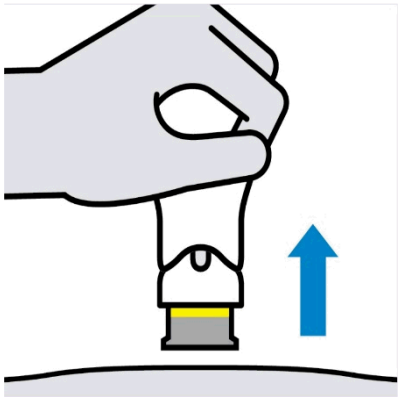
Place straight on skin. Push handle all the way down until purple body is not visible.

DO NOT LIFT PRE-FILLED PEN during injection!
If you do, the needle guard will lock, showing a yellow band, and you will not get the full dose.

You may hear a click when the injection begins. Keep pushing.
If you feel resistance, keep pushing. This is normal.
The medication injects as you push. Do this at a speed that is comfortable for you.



Confirm your injection is complete
Your injection is complete when:
- The purple body is not visible.
- You cannot press the handle down anymore.
- You may hear a click.

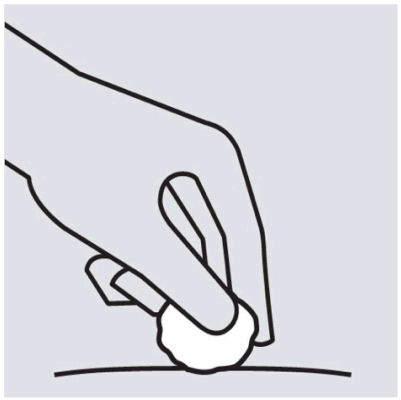


Lift straight up
The yellow band indicates that the needle guard is locked into place.

3. After your injection



Dispose of the pre-filled pen
Put the used pre-filled pen in a sharps disposal container right away after use.
Do not throw away (dispose of) the pre-filled pens in the household trash.
Do not recycle your used sharps disposal container.



Check injection site
There may be a small amount of blood or liquid at the injection site. This is normal. Press a cotton ball or gauze pad to the injection site until any bleeding stops.
Do not rub the injection site.
If needed, cover the injection site with a bandage.

If you receive two 45 mg pre-filled pens for a 90 mg dose, repeat Steps 1-3 with the second pre-filled pen. **Choose a different injection site for the second injection.**

1.7　同種同効品一覧表

販売名	ステラーラ®点滴静注 130 mg，同皮下注 45 mg シリンジ，同皮下注 45 mg バイアル	レミケード®点滴静注用 100
一般名	ウステキヌマブ（遺伝子組換え）	インフリキシマブ（遺伝子組換え）
会社名	ヤンセンファーマ株式会社	田辺ファーマ株式会社
効能又は効果	ステラーラ®点滴静注 130 mg ● 中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る） ● 中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る） 同皮下注 45 mg シリンジ，同皮下注 45 mg バイアル ● 既存治療で効果不十分な下記疾患 尋常性乾癬、乾癬性関節炎 ● 中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る） ● 中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）	既存治療で効果不十分な下記疾患 ● 関節リウマチ（関節の構造的損傷の防止を含む） ● ベーチェット病による難治性網膜ぶどう膜炎 ● 尋常性乾癬、乾癬性関節炎、膿疱性乾癬、乾癬性紅皮症 ● 強直性脊椎炎 ● 腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病 ● 川崎病の急性期 ● 次のいずれかの状態を示すクローン病の治療及び維持療法（既存治療で効果不十分な場合に限る） 中等度から重度の活動期にある患者 外瘻を有する患者 ● 中等症から重症の潰瘍性大腸炎の治療（既存治療で効果不十分な場合に限る）
添付文書改訂日	—	2026 年 4 月

最新の添付文書を参照すること

**2026年４月改訂（第４版） D33
*2025年12月改訂（第３版）

日本標準商品分類番号
87239

貯法：2～8℃に保存
有効期間：3年
規制区分
生物由来製品
劇薬
処方箋医薬品注）

注）注意―医師等の処方箋により使用すること

抗ヒトTNFαモノクローナル抗体製剤
インフリキシマブ（遺伝子組換え）製剤

レミケード®点滴静注用100

REMICADE® for I.V. Infusion

承認番号	21400AMY00013
販売開始	2002年５月

1. 警告

〈効能共通〉

1.1 本剤投与により、結核、敗血症を含む重篤な感染症及び脱髄疾患の悪化等があらわれることがあり、本剤との関連性は明らかではないが、悪性腫瘍の発現も報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上まわると判断される場合にのみ投与すること。また、本剤の投与において、重篤な副作用により、致命的な経過をたどることがあるので、緊急時に十分に措置できる医療施設及び医師のもとで投与し、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。［1.2.1、1.2.2、1.4、2.1、2.2、2.4、8.2、8.7、9.1.1、9.1.2、9.1.4、11.1.1、11.1.2、11.1.4、15.1.4 参照］

1.2 感染症

1.2.1 重篤な感染症

敗血症、真菌感染症を含む日和見感染症等の致死的な感染症があらわれることがあるため、十分な観察を行うなど感染症の発症に注意すること。［1.1、2.1、9.1.1、11.1.1 参照］

1.2.2 結核

播種性結核（粟粒結核）及び肺外結核（髄膜、胸膜、リンパ節等）を含む結核が発症し、死亡例も認められている。結核の既感染者では症状の顕在化及び悪化のおそれがあるため、本剤投与に先立って結核に関する十分な問診及び胸部レントゲン検査に加え、インターフェロン-γ遊離試験又はツベルクリン反応検査を行い、適宜胸部CT検査等を行うことにより、結核感染の有無を確認すること。川崎病患者において、本剤の投与に緊急を要する場合には、少なくとも十分な問診、胸部レントゲン検査等を行うことにより、結核感染の有無を十分に確認すること。また、結核の既感染者には、抗結核薬の投与をした上で、本剤を投与すること。ツベルクリン反応等の検査が陰性の患者において、投与後活動性結核が認められた例も報告されている。［1.1、2.2、8.2、9.1.2、11.1.2 参照］

1.3 本剤投与に関連する反応

1.3.1 Infusion reaction

本剤投与中あるいは投与終了後2時間以内に発現するinfusion reactionのうち、重篤なアナフィラキシー（呼吸困難、気管支痙攣、血圧上昇、血圧低下、血管性浮腫、チアノーゼ、低酸素症、発熱、蕁麻疹等）、痙攣があらわれることがある。本剤は緊急時に十分な対応のできる準備をした上で投与を開始し、投与終了後も十分な観察を行うこと。また、重篤なinfusion reactionが発現した場合には、本剤の投与を中止し、適切な処置を行うこと。［2.3、8.6、8.8、9.1.7、11.1.3、14.2.2 参照］

1.3.2 遅発性過敏症（再投与の場合）

本剤投与後3日以上経過後に重篤なものを含む遅発性過敏症（筋肉痛、発疹、発熱、多関節痛、そう痒、手・顔面浮腫、嚥下障害、蕁麻疹、咽頭痛、頭痛等）があらわれることがある。再投与には遅発性過敏症の発現に備え、十分な観察を行うこと。［2.3、8.6、9.1.7、11.1.7 参照］

1.4 脱髄疾患の臨床症状及び/又は画像診断上の悪化が、本剤を含むTNF抑制作用を有する薬剤であらわれることがある。脱髄疾患（多発性硬化症等）及びその既往歴のある患者には投与しないこととし、脱髄疾患を疑う患者や家族歴を有する患者に投与する場合には、適宜画像診断等の検査を実施するなど、十分な観察を行うこと。［1.1、2.4、9.1.4、11.1.4 参照］

〈関節リウマチ〉

1.5 本剤の治療を行う前に、非ステロイド性抗炎症剤及び他の抗リウマチ薬等の使用を十分勘案すること。また、本剤についての十分な知識とリウマチ治療の経験をもつ医師が使用すること。

〈ベーチェット病による難治性網膜ぶどう膜炎〉

1.6 本剤の治療を行う前に、既存治療薬（シクロスポリン等）の使用を十分勘案すること。また、ベーチェット病による難治性網膜ぶどう膜炎の治療経験を持つ眼科医と本剤について十分な知識を有する内科等の医師が診断と治療に対して十分な連携をとり使用すること。

〈乾癬〉

1.7 本剤の治療を行う前に、既存の全身療法（紫外線療法を含む）の使用を十分勘案すること。また、乾癬の治療経験を持つ医師と本剤について十分な知識を有する医師が連携をとり使用すること。

〈強直性脊椎炎〉

1.8 本剤の治療を行う前に、既存治療薬（非ステロイド性抗炎症剤等）の使用を十分勘案すること。また、本剤についての十分な知識と強直性脊椎炎の診断及び治療の経験をもつ医師が使用すること。

〈腸管型ベーチェット病、神経型ベーチェット病及び血管型ベーチェット病〉

1.9 本剤の治療を行う前に、既存治療薬の使用を十分勘案すること。また、本剤についての十分な知識と腸管型ベーチェット病、神経型ベーチェット病又は血管型ベーチェット病治療の十分な知識・経験をもつ医師が使用すること。

〈川崎病の急性期〉

1.10 本剤の治療を行う前に、免疫グロブリン療法等の実施を十分勘案すること。また、本剤についての十分な知識と川崎病治療の経験をもつ医師が使用すること。

〈クローン病〉

1.11 本剤の治療を行う前に、既存治療薬の使用を十分勘案すること。また、本剤についての十分な知識とクローン病治療の経験をもつ医師が使用すること。

〈潰瘍性大腸炎〉

1.12 本剤の治療を行う前に、既存治療薬の使用を十分勘案すること。また、本剤についての十分な知識と潰瘍性大腸炎治療の経験をもつ医師が使用すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な感染症（敗血症等）の患者［症状を悪化させるおそれがある。］［1.1、1.2.1、9.1.1、11.1.1 参照］

2.2 活動性結核の患者［症状を悪化させるおそれがある。］［1.1、1.2.2、8.2、9.1.2、11.1.2 参照］

2.3 本剤の成分又はマウス由来の蛋白質（マウス型、キメラ型、ヒト化抗体等）に対する過敏症の既往歴のある患者［1.3.1、1.3.2、8.6、8.8、9.1.7、11.1.3、11.1.7、14.2.2 参照］

2.4 脱髄疾患（多発性硬化症等）及びその既往歴のある患者［症状の再燃及び悪化のおそれがある。］［1.1、1.4、9.1.4、11.1.4 参照］

2.5 うっ血性心不全の患者［15.1.2 参照］

3. 組成・性状

3.1 組成

成分・含量（1バイアル中）	有効成分	インフリキシマブ（遺伝子組換え）100mg
	添加剤	精製白糖：500mg ポリソルベート80：0.5mg リン酸二水素ナトリウム一水和物：2.2mg リン酸水素二ナトリウム二水和物：6.1mg その他の添加物としてpH調整剤を含有する

本剤は、マウス骨髄腫由来細胞を用いて製造される。また、製造工程において、培地成分としてウシの脾臓及び血液由来成分（蛋白加水分解物）並びにウシの血液由来成分（血清アルブミン、胎児血清、リポプロテイン、アポトランスフェリン）を使用している。

3.2 製剤の性状

性状	白色の塊（凍結乾燥ケーキ）

4. 効能又は効果

既存治療で効果不十分な下記疾患

○ 関節リウマチ（関節の構造的損傷の防止を含む）
○ ベーチェット病による難治性網膜ぶどう膜炎

○ 尋常性乾癬、乾癬性関節炎、膿疱性乾癬、乾癬性紅皮症
○ 強直性脊椎炎
○ 腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病
○ 川崎病の急性期
○ 次のいずれかの状態を示すクローン病の治療及び維持療法（既存治療で効果不十分な場合に限る）
中等度から重度の活動期にある患者
外瘻を有する患者
○ 中等症から重症の潰瘍性大腸炎の治療（既存治療で効果不十分な場合に限る）

5. 効能又は効果に関連する注意

〈関節リウマチ〉

5.1 過去の治療において、非ステロイド性抗炎症剤及び他の抗リウマチ薬（メトトレキサート製剤を含む）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与を行うこと。また、メトトレキサート製剤に本剤を上乗せすることのリスク・ベネフィットを判断した上で使用すること。

〈ベーチェット病による難治性網膜ぶどう膜炎〉

5.2 過去の治療において、他の薬物療法（シクロスポリン等）等の適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。

〈乾癬〉

5.3 過去の治療において、既存の全身療法（紫外線療法を含む）等の適切な治療を行っても、皮疹が体表面積の10%以上に存在する場合、もしくは難治性の皮疹、関節症状又は膿疱を有する場合に本剤の投与を行うこと。

〈強直性脊椎炎〉

5.4 過去の治療において、他の薬物療法（非ステロイド性抗炎症剤等）等の適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。

〈腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病〉

5.5 過去の治療において、他の薬物療法等の適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。

〈川崎病の急性期〉

5.6 過去の治療において、免疫グロブリン療法等を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。

〈クローン病〉

5.7 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等の適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。なお、寛解維持投与は漫然と行わず経過を観察しながら行うこと。

〈潰瘍性大腸炎〉

5.8 過去の治療において、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等の適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に本剤の投与を行うこと。寛解維持効果は確認されていないため、寛解導入後には本剤の継続投与の必要性を検討し、他の治療法への切替えを考慮すること。

6. 用法及び用量

〈関節リウマチ〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり3mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。なお、6週の投与以後、効果不十分又は効果が減弱した場合には、投与量の増量や投与間隔の短縮が可能である。これらの投与量の増量や投与間隔の短縮は段階的に行う。1回の体重1kg当たりの投与量の上限は、8週間の間隔であれば10mg、投与間隔を短縮した場合であれば6mgとする。また、最短の投与間隔は4週間とする。本剤は、メトトレキサート製剤による治療に併用して用いること。

〈ベーチェット病による難治性網膜ぶどう膜炎〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。

〈乾癬〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。なお、6週の投与以後、効果不十分又は効果が減弱した場合には、投与量の増量や投与間隔の短縮が可能である。これらの投与量の増量や投与間隔の短縮は患者の状態に応じて段階的に行う。1回の体重1kg当たりの投与量の上限は、8週間の間隔であれば10mg、投与間隔を短縮した場合であれば6mgとする。また、最短の投与間隔は4週間とする。

〈強直性脊椎炎〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後6～8週間の間隔で投与を行うこと。

〈腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。なお、6週の投与以後、効果不十分又は効果が減弱した場合には、体重1kg当たり10mgを1回の投与量とすることができる。

〈川崎病の急性期〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを単回点滴静注する。

〈クローン病〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。なお、6週の投与以後、効果が減弱した場合には、投与量の増量又は投与間隔の短縮が可能である。投与量を増量する場合は、体重1kg当たり10mgを1回の投与量とすることができる。投与間隔を短縮する場合は、体重1kg当たり5mgを1回の投与量とし、最短4週間の間隔で投与することができる。

〈潰瘍性大腸炎〉

通常、インフリキシマブ（遺伝子組換え）として、体重1kg当たり5mgを1回の投与量とし点滴静注する。初回投与後、2週、6週に投与し、以後8週間の間隔で投与を行うこと。

〈効能共通〉

なお、本剤投与時には、1.2ミクロン以下のメンブランフィルターを用いたインラインフィルターを通して投与すること。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤と他の生物学的製剤の併用について安全性及び有効性は確立していないので併用を避けること。

〈関節リウマチ〉

7.2 国内及び海外の臨床試験により、メトトレキサート製剤併用での有効性及び安全性が確認されている。国内臨床試験におけるメトトレキサート製剤の併用量は、6mg/週以上であり、メトトレキサート併用時の本剤に対する抗体の産生率は、メトトレキサート非併用時よりも低かった。なお、メトトレキサート製剤以外の抗リウマチ薬併用の有用性は確立していない。［8.8、16.1.5-16.1.7 参照］

7.3 初回、2週、6週投与までは10mg/kg等への増量投与は行わないこと。また、増量により感染症の発現頻度が高まる恐れがあるため、感染症の発現には十分注意すること。10mg/kg等の高用量を初回投与から行うことにより、重篤な感染症の発現頻度が高まったとの報告がある[1)]。

7.4 本剤による効果は、通常投与開始から14週以内に得られることが確認されている。14週以内に全く効果が得られない場合や、増量や投与間隔の短縮を行っても効果が得られない場合には、現在の治療計画の継続を慎重に再考すること。

7.5 本剤とアバタセプト（遺伝子組換え）の併用は行わないこと。海外で実施したプラセボを対照とした臨床試験において、本剤を含む抗TNF製剤とアバタセプト（遺伝子組換え）の併用療法を受けた患者では併用による効果の増強は示されておらず、感染症及び重篤な感染症の発現率が本剤を含む抗TNF製剤のみによる治療を受けた患者での発現率と比べて高かった。

〈乾癬〉

7.6 初回、2週、6週投与までは10mg/kg等への増量投与は行わないこと。また、増量により感染症の発現頻度が高まる恐れがあるため、感染症の発現には十分注意すること。本剤による効果が全く認められない場合や、増量や投与間隔の短縮を行っても症状の改善が認められない場合には、現在の治療計画の継続を慎重に再考すること。

〈腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病〉

7.7 初回、2週、6週投与までは10mg/kgへの増量投与は行わないこと。増量を行っても、症状や検査所見の改善が認められない場合には、現在の治療計画の継続を慎重に再考すること。

〈クローン病〉

7.8 本剤を初回投与後、2週、6週と投与した後、臨床症状や内視鏡所見等により治療効果を評価すること。効果が認められない場合には、さらに継続投与を行っても効果が得られない可能性があり、他の治療法を考慮すること。また、10mg/kgへの増量や投与間隔の短縮は、5mg/kg 8週間隔投与による治療により効果は認められたものの、維持療法中に効果が減弱し、症状の再燃が認められた患者に対して行うこと。増量又は投与間隔の短縮を行っても効果が認められない場合には、他の治療法を考慮すること。

〈潰瘍性大腸炎〉

7.9 本剤を初回投与後、2週、6週と投与した後、8週時点で臨床症状や内視鏡所見等により治療効果を評価すること。効果が認められない場合には、さらに継続投与を行っても効果が得られない可能性があり、他の治療法を考慮すること。

8. 重要な基本的注意

8.1 本剤は血中濃度が長期にわたり持続するため（5mg/kg投与時は少なくとも8～12週間）、この間には副作用の発現に注意すること。また、他の生物製剤との切り替えの際も注意すること。

8.2 本剤投与に先立って結核に関する十分な問診及び胸部レントゲン検査に加え、インターフェロン-γ遊離試験又はツベルクリン反応検査を行い、適宜胸部CT検査等を行うことにより、結核感染の有無を確認すること。川崎病患者において、本剤の投与に緊急を要する場合には、少なくとも十分な問診、胸部レントゲン検査等を行うことにより、結核感染の有無を十分に確認すること。
また、本剤投与中も、胸部レントゲン検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、患者に対し、結核を疑う症状が発現した場合（持続する咳、発熱等）には速やかに主治医に連絡するよう説明すること。[1.1、1.2.2、2.2、9.1.2、11.1.2 参照]

8.3 本剤を含む抗TNF製剤によるB型肝炎ウイルスの再活性化が報告されているので、本剤投与に先立って、B型肝炎ウイルス感染の有無を確認すること。[9.1.3 参照]

8.4 本剤を投与した後、発熱、咳嗽、呼吸困難等の間質性肺炎の症状があらわれた場合には速やかに主治医に連絡するよう患者に説明すること。[9.1.5、11.1.5 参照]

8.5 本剤治療中は、生ワクチン接種を行わないこと。また、本剤の投与と生ワクチン接種との間隔は十分にあけることが望ましい。やむを得ず生ワクチン接種から本剤の投与まで十分な間隔をあけることができない場合には、リスク・ベネフィットを慎重に判断した上で使用すること。生ワクチンによる感染症発現の可能性が否定できない。

8.6 本剤投与中はinfusion reactionに対する適切な薬剤治療（アドレナリン、副腎皮質ホルモン剤、抗ヒスタミン剤又はアセトアミノフェン等）や緊急処置を直ちに実施できるよう十分な体制のもとで、投与を開始し、投与終了後も十分な観察を行うこと。また、遅発性過敏症（3日以上経過後）があらわれることがあるので、患者に十分説明し、発疹、発熱、そう痒、手・顔面浮腫、蕁麻疹、頭痛等が発現した場合、主治医に連絡するよう指示するなど適切な対応をとること。[1.3.1、1.3.2、2.3、8.8、9.1.7、11.1.3、11.1.7、14.2.2 参照]

8.7 臨床試験における投与後3年間の追跡調査で、悪性リンパ腫等の悪性腫瘍の発現が報告されている。慢性炎症性疾患のある患者に長期の免疫抑制剤を投与した場合、感染症や悪性リンパ腫の発現の危険性が高まることが報告されている。また、本剤を含む抗TNF製剤を使用した小児や若年成人においても、悪性リンパ腫等の悪性腫瘍が報告されている。本剤に起因するか明らかでないが、悪性腫瘍等の発現には注意すること。[1.1、15.1.4 参照]

8.8 本剤はマウス蛋白由来部分があるため、ヒトには異種蛋白であり、投与後、本剤に対する抗体が産生されることがある。臨床試験において本剤に対する抗体の産生が確認された患者群は、抗体が産生されなかった患者群に比べ、infusion reactionの発現が多い傾向にあり、また、本剤の血中濃度の持続が短くなる傾向がみられ、血中濃度が低下した患者では効果の減弱の可能性がある。[1.3.1、2.3、7.2、8.6、9.1.7、11.1.3、14.2.2、16.1.4-16.1.9、16.1.11-16.1.16、16.6.1 参照]

8.9 本剤を投与した患者において、乾癬が悪化又は新規発現したとの報告がある。重症な場合には本剤投与の中止を考慮すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 感染症（重篤な感染症を除く）の患者又は感染症が疑われる患者
適切な処置と十分な観察が必要である。本剤は免疫反応を減弱する作用を有し、正常な免疫応答に影響を与える可能性がある。[1.1、1.2.1、2.1、11.1.1 参照]

9.1.2 結核の既感染者（特に結核の既往歴のある患者及び胸部レントゲン上結核治癒所見のある患者）又は結核感染が疑われる患者

(1) 結核の既感染者は、問診及び胸部レントゲン検査等を定期的（投与開始後2ヵ月間は可能な限り1ヵ月に1回、以降は適宜必要に応じて）に行うことにより、結核症状の発現に十分に注意すること。結核を活動化させるおそれがある。[1.1、1.2.2、2.2、8.2、11.1.2 参照]

(2) 結核の既往歴を有する場合及び結核が疑われる場合には、結核の診療経験がある医師に相談すること。以下のいずれかの患者には、原則として抗結核薬の投与をした上で、本剤を投与すること。
- 胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
- 結核の治療歴（肺外結核を含む）を有する患者
- インターフェロン-γ遊離試験やツベルクリン反応検査などの検査により、既感染が強く疑われる患者
- 結核患者との濃厚接触歴を有する患者

[1.1、1.2.2、2.2、8.2、11.1.2 参照]

9.1.3 B型肝炎ウイルスキャリアの患者又は既往感染者（HBs抗原陰性、かつHBc抗体またはHBs抗体陽性）
肝機能検査値や肝炎ウイルスマーカーのモニタリングを行うなど、B型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。本剤を含む抗TNF製剤が投与されたB型肝炎ウイルスキャリアの患者又は既往感染者において、B型肝炎ウイルスの再活性化が報告されている。なお、これらの報告の多くは、他の免疫抑制作用をもつ薬剤を併用投与した患者に起きている。[8.3 参照]

9.1.4 脱髄疾患が疑われる徴候を有する患者及び家族歴のある患者

(1) 脱髄疾患が疑われる徴候を有する患者については、神経学的評価や画像診断等の検査を行い、慎重に危険性と有益性を評価した上で本剤適用の妥当性を検討し、投与後は十分に観察を行うこと。脱髄疾患発現のおそれがある。[1.1、1.4、2.4、11.1.4 参照]

(2) 脱髄疾患の家族歴のある患者は、適宜画像診断等の検査を実施し、十分に注意すること。脱髄疾患発現のおそれがある。[1.1、1.4、2.4、11.1.4 参照]

9.1.5 間質性肺炎の既往歴のある患者
定期的に問診を行うなど、注意すること。間質性肺炎が増悪又は再発することがある。[8.4、11.1.5 参照]

9.1.6 重篤な血液疾患（汎血球減少、再生不良性貧血等）の患者又はその既往歴のある患者
血液疾患が悪化するおそれがある。[11.1.9 参照]

9.1.7 本剤投与経験のある患者
Infusion Reaction、遅発性過敏症が発現する可能性がある。[1.3.1、1.3.2、2.3、8.6、8.8、11.1.3、11.1.7、14.2.2 参照]

9.5 妊婦

9.5.1 妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上まわると判断される場合にのみ投与すること。本剤投与による生殖発生毒性試験は実施されていない（本剤がヒトTNFα特異的で動物実験が実施できないため）。また、マウスTNFαを中和する抗体投与により、マウスを用いて検討された結果では、催奇形性、母体毒性、胎児毒性は認められていない。

9.5.2 本剤は胎盤通過性があるとの報告がある。従って、本剤の投与を受けた患者からの出生児においては、感染のリスクが高まる可能性があるため、生ワクチンを接種する際には注意が必要である。

9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

9.7 小児等
〈クローン病及び潰瘍性大腸炎〉

9.7.1 6歳未満の幼児等を対象とした国内臨床試験は実施していないため、これらの患者には治療上の有益性が危険性を上回ると判断される場合のみ投与し、副作用の発現に十分注意すること。

〈川崎病の急性期〉

9.7.2 1歳未満の乳児を対象とした国内臨床試験は実施していないため、これらの患者には治療上の有益性が危険性を上回ると判断される場合のみ投与し、副作用の発現に十分注意すること。

〈上記以外の効能〉

9.7.3 小児等を対象とした臨床試験は実施していない。

9.8 高齢者
感染症等の副作用の発現に留意し、十分な観察を行うこと。一般に生理機能（免疫機能等）が低下している。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 感染症（3.5%）
敗血症、肺炎（ニューモシスティス肺炎を含む）、真菌感染症、脳炎、髄膜炎（リステリア菌性髄膜炎を含む）、骨髄炎等の重篤な感染症（日和見感染症を含む）があらわれることがある。なお、死亡に至った症例の多くは、感染症によるものであった。[1.1、1.2.1、2.1、9.1.1 参照]

11.1.2 結核（0.3%）
結核の発症は、投与初期からあらわれる可能性がある。また、肺外結核（髄膜、胸膜、リンパ節等）もあらわれることがあることからその可能性も十分考慮した観察を行うこと。[1.1、1.2.2、2.2、8.2、9.1.2 参照]

11.1.3 重篤なinfusion reaction（0.6%）
ショック、アナフィラキシー（呼吸困難、気管支痙攣、血圧上昇、血圧低下、血管性浮腫、チアノーゼ、低酸素症、発熱、蕁麻疹等の重篤な副作用）、痙攣があらわれることがある。
また、infusion reactionに引き続き脳出血、脳梗塞があらわれることがある。[1.3.1、2.3、8.6、8.8、9.1.7、14.2.2 参照]

11.1.4 脱髄疾患（0.1%）
多発性硬化症、視神経炎、横断性脊髄炎、ギラン・バレー症候群等があらわれることがある。[1.1、1.4、2.4、9.1.4 参照]

11.1.5 間質性肺炎（0.5%）
発熱、咳嗽、呼吸困難等の呼吸器症状に十分に注意し、異常が認められた場合には、速やかに胸部レントゲン検査、胸部CT検査及び血液ガス検査等を実施し、本剤及びメトトレキサート製剤の投与を中止するとともにニューモシスティス肺炎との鑑別診断（β-Dグルカンの測定等）を考慮に入れ、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。主としてメトトレキサート製剤併用時において、間

質性肺炎を発現し致命的な経過をたどった症例が報告されている。[8.4、9.1.5 参照]

11.1.6 肝機能障害（0.1%）
AST、ALT、γ-GTP、LDH等の著しい上昇を伴う重篤な肝機能障害があらわれることがある。

11.1.7 遅発性過敏症（0.6%）
筋肉痛、発疹、発熱、多関節痛、そう痒、手・顔面浮腫、嚥下障害、蕁麻疹、咽頭痛、頭痛等を伴う遅発性過敏症（3日以上経過後）があらわれることがある。[1.3.2、2.3、8.6、9.1.7 参照]

11.1.8 抗dsDNA抗体の陽性化を伴うループス様症候群（0.4%）
抗dsDNA抗体が陽性化し、関節痛、筋肉痛、皮疹等の症状があらわれることがある。このような場合には、投与を中止すること。

11.1.9 重篤な血液障害（0.1%）
汎血球減少、血小板減少、白血球減少、顆粒球減少、血球貪食症候群、血小板減少性紫斑病があらわれることがある。[9.1.6 参照]

11.1.10 横紋筋融解症（頻度不明）
脱力感、筋肉痛、CK上昇、血中及び尿中ミオグロビン上昇に注意し、このような症状があらわれた場合には投与を中止し、適切な処置を行うこと。

****11.1.11 自己免疫性肝炎**（頻度不明）

11.2 その他の副作用

	5%以上	1%以上～5%未満	1%未満	頻度不明
精神・神経系	頭痛	浮動性めまい、感覚鈍麻、異常感覚	頭部不快感、体位性めまい、知覚過敏、失神、嗅覚錯誤、味覚異常、神経痛、不随意性筋収縮、片頭痛、振戦、運動過多、ジスキネジー、脳梗塞、協調運動異常、不眠症、不安、神経過敏、うつ病、感情不安定、多幸気分、錯乱、傾眠（眠気）	多発性神経障害、ニューロパシー、てんかん発作
血液		貧血（鉄欠乏性貧血、溶血性貧血）、カリウム減少、血小板数増加	リンパ節炎、脾腫、単球減少症、リンパ球減少症、リンパ球増加症、単球増加症、白血球増加症、好中球増加症、好酸球増加症、赤血球異常、低カリウム血症、好酸球数減少、骨髄球数増加、アミラーゼ増加、総蛋白減少、総蛋白増加、アルブミン減少、クロール減少、ナトリウム減少、血沈亢進、リンパ球形態異常（異形リンパ球）、リンパ節症、後骨髄球数増加、尿酸増加、カリウム増加、CRP増加、ヘマトクリット減少	血栓性血小板減少性紫斑病
循環器		ほてり、潮紅、高血圧、低血圧、動悸、血圧低下、血圧上昇	血腫、蒼白、末梢性虚血、徐脈、不整脈、頻脈、心室性期外収縮、狭心症、心不全、心拍数増加	血管炎(IgA血管炎)
呼吸器	気道感染、咽喉頭炎	呼吸困難、気管支炎、咳嗽、鼻炎、副鼻腔炎	発声障害、咽喉絞扼感、鼻出血、胸膜炎、胸水、喘息、気管支痙攣、胸部X線（CT）異常、PaO_2低下、KL-6増加、扁桃炎	間質性肺線維症
肝臓		ALP増加	脂肪肝、肝炎、胆嚢炎、肝腫大、高ビリルビン血症	
泌尿器	血尿（尿潜血）	尿路感染、尿中ブドウ糖陽性、尿中蛋白陽性、BUN増加、尿沈渣	腎盂腎炎、排尿困難、尿中白血球陽性、頻尿、クレアチニン増加、尿中ウロビリノーゲン増加、膀胱炎	
消化器	悪心	嘔吐、下痢、腹痛、便秘、胃腸炎	上腹部痛、嚥下障害、逆流性食道炎、腸閉塞、腸管狭窄、消化不良、血便、腸管穿孔、胃炎、痔核、肛門周囲痛、憩室炎、腹部膨満、胃ポリープ、胃潰瘍、腹膜炎、腹部不快感、腸炎、胃不快感、軟便、放屁	
		口内炎、歯周病	口腔内潰瘍形成、歯痛、口唇炎、口腔内痛、齲歯、唾液腺炎、口渇、舌炎	
皮膚	発疹（膿疱性皮疹、斑状皮疹、斑状丘疹状皮疹、小水疱性皮疹、そう痒性皮疹、湿疹、紅斑性皮疹、頭部粃糠疹、丘疹、血管炎性皮疹）	白癬、皮膚炎（脂漏性皮膚炎、水疱性皮膚炎、乾癬様皮膚炎、ざ瘡様皮膚炎）、毛包炎、そう痒症、蕁麻疹、紅斑（発赤）、多汗症	麦粒腫、せつ、皮膚真菌感染、皮膚裂傷、皮膚嚢腫、ざ瘡、皮膚乾燥、皮膚変色、皮膚剥脱、脱毛症、乾癬、斑状出血、点状出血、皮膚潰瘍、脂漏、過角化、光線過敏性反応、皮膚腫瘤、多毛症、アトピー性皮膚炎	
投与部位			注射部位反応（注射部位疼痛、注射部位炎症、注射部位腫脹、注射部位出血、注射部位そう痒感）	
眼			眼内炎、涙器障害、角膜炎、眼瞼炎、視覚障害、眼痛、眼球乾燥、羞明、強膜炎、緑内障、眼圧上昇、眼脂、結膜炎、結膜充血、視野欠損、網膜静脈閉塞	
耳			耳痛、回転性めまい、耳鳴、耳不快感（耳閉感）、耳感染（外耳炎、中耳炎、迷路炎）	
筋・骨格系		関節痛、筋痛	関節腫脹、背部痛、筋骨格硬直、頚部痛、関節炎、骨痛、腱炎、筋力低下、滑液包炎、CK増加、筋骨格痛	皮膚筋炎、多発性筋炎
抵抗機構	自己抗体陽性（抗DNA抗体陽性、抗カルジオリピン抗体陽性、抗核抗体陽性）、ウイルス感染（帯状疱疹、単純ヘルペスフルエンザ様疾患、インフルエンザ）	膿瘍	免疫グロブリン増加、爪周囲炎、限局性感染、サイトメガロウイルス抗原陽性、食道カンジダ症、蜂巣炎	ニューモシスティス症、サルモネラ症、イドーコシス、非結核性マイコバクテリア感染（非結核性抗酸菌症）、クリプトスポリジウム症
代謝		高コレステロール血症	糖尿病、高血糖、抗利尿ホルモン不適合分泌、コレステロール減少、トリグリセリド増加	

	5%以上	1%以上～5%未満	1%未満	頻度不明
その他	発熱	悪寒、熱感、倦怠感、疲労、胸痛、疼痛、浮腫（末梢性浮腫、顔面浮腫、全身性浮腫、眼窩周囲浮腫、血管性浮腫、咽頭浮腫、喉頭浮腫）	膣感染、勃起不全、乳房肥大、亀頭包皮炎、不規則月経、膣出血、性器分泌物（白帯下）、無力症、不快感、胸部不快感、嚢胞、食欲不振、食欲亢進、過敏症、体重増加、体重減少、子宮平滑筋腫、リビドー減退、末梢腫脹	

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 溶解方法

本剤は用時溶解とすること。（溶解後3時間以内に投与開始をすること。）

(1) ゴム栓をエタノール綿等で清拭した後、21-Gあるいはさらに細い注射針を用いて、1バイアル当たり10mLの日局注射用水（日局生理食塩液も使用可）を静かに注入すること。その際に陰圧状態でないバイアルは使用しないこと。

(2) バイアルを回転させながら緩やかに溶解し、溶解後は5分間静置すること。抗体蛋白が凝集するおそれがあるため、決して激しく振らず、長時間振り混ぜないこと。

(3) 蛋白製剤なので、溶解後の性状として、無色から薄黄色及び乳白色をしており、僅かながら半透明の微粒子を含むことがあるが、力価等に影響はない。変色、異物、その他の異常を認めたものは使用しないこと。

(4) 溶解後の残液の再使用や保存は行わないこと。

14.1.2 希釈方法

患者の体重当たりで計算した必要量を成人は約250mL、体重が25kg未満の小児は約50mL、25kg以上の小児は約100mLの日局生理食塩液に希釈すること。体重が100kgを超える患者に投与する場合には、希釈後のインフリキシマブ濃度が4mg/mLを超えないよう、日局生理食塩液の量を調整すること。ブドウ糖注射液等を含め日局生理食塩液以外の注射液は用いないこと。日局生理食塩液で希釈する際は、溶解液を緩徐に注入し、混和の際も静かに行うこと。希釈後のインフリキシマブ濃度は、0.4～4mg/mLとすること。

14.2 薬剤投与時の注意

14.2.1 投与器具

本剤は無菌・パイロジェンフリーのインラインフィルター（ポアサイズ1.2ミクロン以下）を用いて投与すること。

14.2.2 投与経路及び投与速度

本剤は独立したラインにて投与するものとし、他の注射剤、輸液等と混合しないこと（ブドウ糖注射液等の汎用される注射液でも配合変化が確認されているため）。また、原則、2時間以上をかけて緩徐に点滴静注すること。

なお、6週の投与以後、それまでの投与でinfusion reactionが認められなければ、点滴速度を上げて点滴時間を短縮することができる。ただし、平均点滴速度は1時間当たり5mg/kgを投与する速度を超えないこと（臨床試験において投与経験がない）。

また、点滴時間を短縮した際にinfusion reactionが認められた場合には、次回以降の投与では、点滴時間を短縮せずに投与すること。［1.3.1、2.3、8.6、8.8、9.1.7、11.1.3 参照］

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 本剤の臨床試験は、国内では62週間（1年）まで、海外では102週間（2年）までの期間で実施されている。また、本剤の長期使用に関する特定使用成績調査は2年間までの期間で実施されている。これらの期間を超えた本剤の長期投与時の安全性は確立していない。

15.1.2 150例の中等度から重度のうっ血性心不全の患者（左室駆出率35%以下で、NYHA心機能分類Ⅲ/Ⅳ度）に、プラセボ及び本剤5、10mg/kgを初回、2週後、6週後に3回投与した海外での臨床試験を実施した。その結果、本剤投与群、特に10mg/kg群において心不全症状の悪化及び死亡が高率に認められたとの報告がある。初回投与後28週時点において、10mg/kg群で3例、5mg/kg群で1例の死亡が認められ、プラセボ群では死亡例はなかった。また、症状悪化による入院は、10mg/kg群51例中11例、5mg/kg群50例中3例、プラセボ群49例中5例であった。さらに、1年後の評価における死亡例は、10mg/kg群で8例であったのに対し、5mg/kg群及びプラセボ群ではそれぞれ4例であった。［2.5 参照］

15.1.3 乾癬患者において、本剤と紫外線療法又は既存の全身治療との併用に対する有効性と安全性は確立していない（使用経験がない）。

15.1.4 本剤の臨床試験及び臨床試験終了後3年間又は5年間の追跡調査において、悪性リンパ腫、乳癌、黒色腫、扁平上皮癌、直腸腺癌、基底細胞癌及び皮膚癌等が169例に報告されている。本剤投与と悪性腫瘍発現の関連性を検討するため、実際に悪性腫瘍が認められた例数並びに大規模なデータベースから抽出した同一背景を有する一般集団からの予測例数を表1～3に示した。この予測例数は、症例毎の性、年齢、追跡期間等よりNIH SEERデータベース（National Institute of Health（NIH）Surveillance, Epidemiology, and End Results（SEER）database）から推定した値を用いた。表1のクローン病患者での比較では、本剤投与群における悪性腫瘍の予測例数14.49例に対し観察例数は21例であった。一方、プラセボ群においては予測例数0.20例に対し観察例数は1例であった。［1.1、8.7 参照］

表1.クローン病全試験での悪性腫瘍の観察例数及び予測例数

クローン病全試験※a	プラセボ投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	97	0	0.01
b.非黒色腫性皮膚癌	96	1	NA
c.上記以外の悪性腫瘍	96	1	0.19
悪性腫瘍計（a＋c）※b	96	1	0.20
クローン病全試験※a	レミケード投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	4094	2	0.65
b.非黒色腫性皮膚癌	4085	8	NA
c.上記以外の悪性腫瘍	4055	19	13.85
悪性腫瘍計（a＋c）※b	4055	21	14.49

※a：既に終了したクローン病試験の試験期間中及び3年間の長期安全性追跡調査での発現例数を集計

※b：NIH SEER databaseに含まれていない非黒色腫性皮膚癌については除外

また、関節リウマチ患者での悪性腫瘍の観察例数及び予測例数を表2に示した。本剤投与群では予測例数52.37例に対し観察例数は50例、プラセボ群では、予測例数13.61例に対し観察例数は10例であった。

表2.関節リウマチ全試験での悪性腫瘍の観察例数及び予測例数

関節リウマチ全試験※a	プラセボ投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	1626	0	0.46
b.非黒色腫性皮膚癌	1611	6	NA
c.上記以外の悪性腫瘍	1604	10	13.16
悪性腫瘍計（a＋c）※b	1604	10	13.61
関節リウマチ全試験※a	レミケード投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	6391	9	1.79
b.非黒色腫性皮膚癌	6357	24	NA
c.上記以外の悪性腫瘍	6343	41	50.80
悪性腫瘍計（a＋c）※b	6331	50	52.37

※a：既に終了した関節リウマチ試験の試験期間中及び3年間又は5年間の長期安全性追跡調査での発現例数を集計

※b：NIH SEER databaseに含まれていない非黒色腫性皮膚癌については除外

また、全臨床試験における悪性腫瘍の観察例数及び予測例数を表3に示した。本剤投与群の予測例数105.18例に対し観察例数は106例、プラセボ群では予測例数19.46例に対して観察例数が15例であった。

表3.全試験での悪性腫瘍の観察例数及び予測例数

全試験※a	プラセボ投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	2906	1	0.72
b.非黒色腫性皮膚癌	2887	12	NA
c.上記以外の悪性腫瘍	2877	14	18.75
悪性腫瘍計（a＋c）※b	2877	15	19.46
全試験※a	レミケード投与例		
	全例追跡期間（人・年）	悪性腫瘍観察例数	悪性腫瘍予測例数
a.悪性リンパ腫	17852	14	4.13
b.非黒色腫性皮膚癌	17721	67	NA
c.上記以外の悪性腫瘍	17720	92	101.30
悪性腫瘍計（a＋c）※b	17707	106	105.18

※a：既に終了した試験の試験期間中及び3年間又は5年間の長期安全性追跡調査での発現例数を集計
※b：NIH SEER databaseに含まれていない非黒色腫性皮膚癌については除外

15.2 非臨床試験に基づく情報

本剤はヒト及びチンパンジーのTNFαのみに結合能を有し、ラットやカニクイザル等の一般的に動物実験に使用される動物種のTNFαと結合しない。このため、がん原性試験は実施されていない。

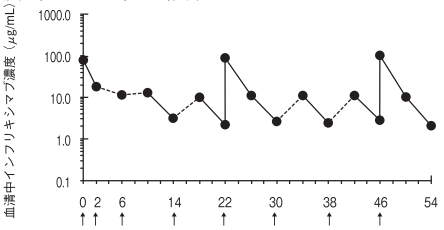
16. 薬物動態

16.1 血中濃度

〈クローン病〉

16.1.1 反復投与における薬物動態

国内クローン病患者に本剤を5mg/kgの用量で3回（0、2、6週）持続静脈内投与後、10週評価時に効果が認められた患者を対象に14週以降8週間隔で投与した時の薬物動態を検討した。8週間隔投与例の投与前の血清中インフリキシマブ濃度（メジアン）は維持された。



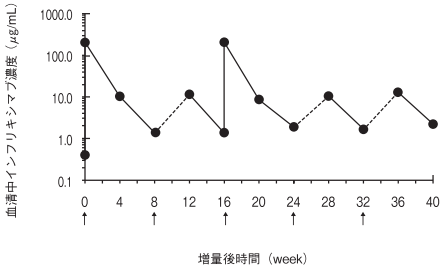
クローン病患者にレミケード5mg/kgを複数回持続静脈内投与した時の8週間隔投与群の血清中インフリキシマブ濃度推移（メジアン，n=31～38，0，22，46週は投与前および投与終了1時間後も表示）　↑：レミケード投与

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre	54週
投与量	5mg/kg（n＝31～38）	平均値±標準偏差	80.4±16.9	3.1±2.4	2.6±2.1	2.0±1.6
		メジアン	78.9	3.1	2.6	2.0

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

16.1.2 増量投与における薬物動態

5mg/kg 8週間隔投与で効果が維持できない患者の5mg/kg投与8週後の血清中インフリキシマブ濃度（メジアン）は0.30μg/mLであったが、これらの患者に10mg/kgを投与した場合、10mg/kg投与8週後の血清中インフリキシマブ濃度（メジアン）は1.29μg/mLまで上昇した。



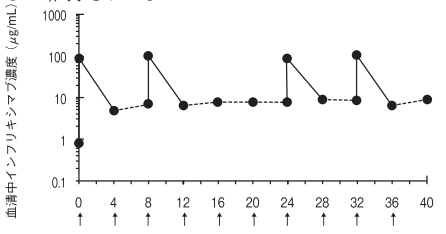
5mg/kg 8週間隔投与で効果が維持できないクローン病患者にレミケード10mg/kgを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=26～39，0，16週は投与前および投与終了1時間後も表示）
↑：レミケード投与

薬物動態パラメータ			増量0週Cpre	増量0週C_{1H}	増量8週Cpre	増量16週Cpre	増量40週
投与量	10mg/kg（n＝26～39）	平均値±標準偏差	1.45±2.67	199.23±41.71	3.24±5.10	3.73±5.85	4.10±5.58
		メジアン	0.30	191.24	1.29	1.31	2.18

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

16.1.3 投与間隔短縮時における薬物動態

5mg/kg 8週間隔投与で効果が維持できない患者19例に5mg/kg 4週間隔投与を行ったときの4週後の血清中濃度は、投与間隔短縮前と比較して増加した。また、血清中濃度は40週まで維持された。



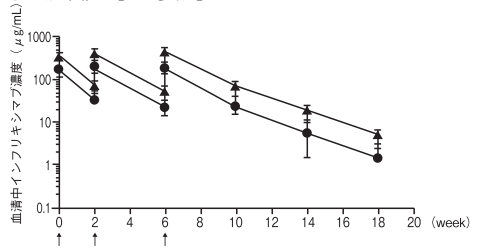
クローン病患者にレミケード5mg/kgを4週間隔で持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=4～19，4週間隔投与移行時点を基点とした）↑：レミケード投与

薬物動態パラメータ※			短縮0週Cpre	短縮0週C_{1H}	短縮4週Cpre	短縮8週Cpre	短縮40週
投与量	5mg/kg（n＝4～19）	平均値±標準偏差	1.83±2.74	85.50±8.65	6.49±6.15	8.96±7.25	14.73±9.20
		メジアン	0.80	86.75	4.90	6.90	8.70

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）
※：投与間隔短縮移行時を0週として集計した。

16.1.4 単回及び反復投与における薬物動態

5mg/kgの単回投与では最高血中濃度（Cmax）の中央値は118μg/mL、分布容積（Vd値）の中央値は3.0L、消失半減期は9.5日であった。臨床試験において、患者の性、年齢、体重、肝及び腎機能等の背景別の薬物動態的な差は認められなかった。副腎皮質ホルモン剤を使用した患者では、使用しない患者に対してVd値の有意な増加（17%）が認められたが、副腎皮質ホルモン剤が電解質バランスに影響するために、体液貯留へ作用した結果と考えられた。5mg/kgの単回投与を受けた20例では2例に本剤に対する抗体が検出された。瘻孔を形成している疾患の患者に本剤5mg/kgを初回、2週後、6週後に反復投与した後の蓄積性はなかった。本剤のクリアランスは、患者のクレアチニン値あるいはAST、ALTと相関は認められず、腎機能・肝機能障害者における動態の差は認められなかった。5mg/kgの反復投与を受けた31例では1例に本剤に対する抗体が検出された（外国人における成績）。[8.8 参照]



↑：レミケード投与
—●—：5mg/kg（n＝28～30）
—▲—：10mg/kg（n＝29～32）

外瘻を有するクローン病患者にレミケードを3回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン±四分位間領域）

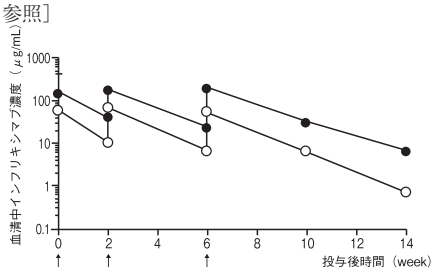
薬物動態パラメータ			0週C_{1H}	2週Cpre	6週Cpre	14週
投与量	5mg/kg (n＝28～30)	メジアン 四分位間領域	168 113-206	33.7 26.7-46.4	21.8 13.8-33.3	5.4 1.4-10.6
	10mg/kg (n＝29～32)	メジアン 四分位間領域	359.5 274-419	75.1 54.1-93.7	50.6 31.7-69.1	17.6 9.3-23.6

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

〈関節リウマチ〉

16.1.5 反復投与における薬物動態

メトトレキサート併用下（6mg/週以上）で、本剤3、10mg/kgを初回、2週後、6週後に反復投与したときの血清中濃度は用量にほぼ比例して増加した（二重盲検比較試験）。また、性、年齢、副腎皮質ホルモン剤あるいは非ステロイド性抗炎症剤併用による背景別の薬物動態の差はみられなかったが、肥満度（BMI）の増加に伴って血清中濃度が増加する傾向がみられた。肝又は腎機能障害を有する患者に薬物動態の差が存在するか否かは不明である。3mg/kgの反復投与を受けた49例では2例、10mg/kgの反復投与を受けた50例では4例に、本剤に対する抗体が検出された。［7.2、8.8参照］



↑：レミケード投与
－○－：3mg/kg（n＝49）
－●－：10mg/kg（n＝48～51）

関節リウマチ患者にレミケードをメトトレキサート併用下（6mg/週以上）3回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン）

薬物動態パラメータ			0週C_{1H}	2週Cpre	6週Cpre	14週
投与量	3mg/kg (n＝49)	平均値±標準偏差 メジアン	47.9±11.3 47.5	11.5±4.1 10.8	5.6±4.1 4.8	0.8±1.1 0.5
	10mg/kg (n＝48～51)	平均値±標準偏差 メジアン	168.4±48.6 168.3	35.6±15.2 33.7	22.3±13.7 20.6	5.4±5.8 3.6

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

16.1.6 増量投与における薬物動態

メトトレキサート併用下（6mg/週以上）で、本剤3mg/kgを初回、2週後、6週後に持続静脈内投与し、引き続き3mg/kg、6mg/kgあるいは10mg/kgを8週間隔で反復投与したときの血清中濃度は用量にほぼ比例して増加した（増量試験）。3mg/kg投与を受けた99例では27例、6mg/kg投与を受けた104例では24例、10mg/kg投与を受けた104例では13例に、本剤に対する抗体が検出された。［7.2、8.8参照］

薬物動態パラメータ			0週C_{1H}	14週C_{1H}	22週Cpre	54週
投与量	3mg/kg (n＝86～99)	平均値±標準偏差 メジアン	57.77±14.23 58.14	60.82±13.60 60.35	0.85±0.98 0.50	0.90±1.13 0.44
	6mg/kg (n＝91～104)	平均値±標準偏差 メジアン	58.86±11.74 58.52	110.94±23.83 113.41	2.18±2.30 1.81	2.88±2.80 2.28
	10mg/kg (n＝95～104)	平均値±標準偏差 メジアン	58.23±11.34 57.16	188.70±39.61 186.12	4.73±4.78 3.13	6.50±6.26 5.47

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

本剤3mg/kgあるいは6mg/kgを8週間隔で反復投与したとき、投与22週時点でACR基準20%改善に達しなかった症例に対して、投与間隔を4週に短縮した場合の推定血清中インフリキシマブ濃度（定常状態の血清中トラフ濃度）注1）は、3mg/kgで3.35［0.83～10.46］、6mg/kgで7.19［1.27～21.62］μg/mL（中央値［最小値～最大値］）であった。

注1）増量試験の患者（327例、5104点）を対象とした母集団薬物動態解析（NONMEM version VI）に基づく薬物動態パラメータを用いたシミュレーション結果

16.1.7 反復投与における薬物動態

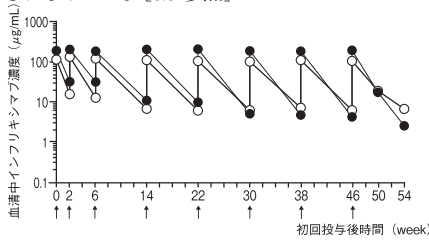
欧米第Ⅲ相試験（ATTRACT試験）において、メトトレキサート併用下（12.5mg/週以上）で、本剤3、10mg/kgを初回、2週後、6週後に持続静脈内投与し、引き続き4週間隔あるいは8週間隔で102週間反復投与した維持治療期にも蓄積性はなく、安定した血清中濃度を長期間にわたり維持することが観察された。3mg/kgの反復投与（4週間隔）を受けた73例では10例、3mg/kgの反復投与（8週間隔）を受けた71例では8例、10mg/kgの反復投与（4週間隔）を受けた74例では1例、10mg/kgの反復投与（8週間隔）を受けた77例では6例に、本剤に対する抗体が検出された（外国人における成績）。［7.2、8.8参照］

注2）本剤の承認最大用量は1回10mg/kgである。

〈ベーチェット病による難治性網膜ぶどう膜炎〉

16.1.8 反復投与における薬物動態

本剤5、10mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週後まで反復投与したときの血清中濃度は投与量の増加に伴って高くなり、安定した血清中濃度を長期間にわたり維持することが観察された。本試験では5、10mg/kgの反復投与を受けた8例において本剤に対する抗体は検出されなかった。［8.8参照］



↑：レミケード投与
－○－：5mg/kg（n＝3～4）
－●－：10mg/kg（n＝3～4）

ベーチェット病による難治性網膜ぶどう膜炎患者にレミケードを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン）

薬物動態パラメータ			0週C_{1H}	2週Cpre	6週Cpre	30週Cpre	54週
投与量	5mg/kg (n＝3～4)	平均値±標準偏差 メジアン	114.9±20.3 119.0	15.9±9.9 15.7	14.3±7.7 13.3	6.7±4.5 6.3	6.8±4.7 7.0
	10mg/kg (n＝3～4)	平均値±標準偏差 メジアン	193.1±17.2 185.9	32.5±22.7 32.9	26.0±17.6 32.1	5.9±6.3 5.2	4.8±6.1 2.6

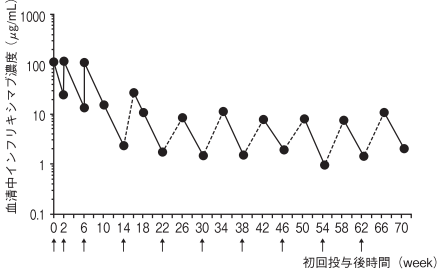
C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

注3）本剤の承認最大用量は1回5mg/kgである。

〈乾癬〉

16.1.9 反復投与における薬物動態

尋常性乾癬患者と乾癬性関節炎患者に本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で62週後まで投与したとき、安定した血清中濃度を維持することが観察された（検証的試験及び継続投与試験）。5mg/kgの反復投与を受けた35例中8例に、本剤に対する抗体が検出された。尋常性乾癬患者、乾癬性関節炎患者、膿疱性乾癬患者及び乾癬性紅皮症患者に本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週後まで投与したとき、14週後から54週後までの投与8週後の血清中濃度（中央値）は0.39μg/mLから2.27μg/mLの範囲で推移した（長期投与試験）。5mg/kgの反復投与を受けた64例中19例に、本剤に対する抗体が検出された。［8.8参照］



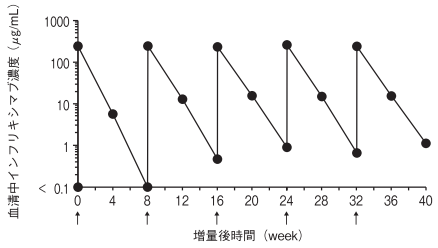
尋常性乾癬患者と乾癬性関節炎患者にレミケード5mg/kgを複数回持続静脈内投与したときの血清中インフリキシマブ濃度推移（メジアン，n=27～35）
↑：レミケード投与

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre	70週
投与量	5mg/kg (n＝27～35)	平均値±標準偏差 メジアン	97.18±19.40 98.33	3.34±2.95 2.45	2.16±2.18 1.48	2.22±2.26 2.09

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

16.1.10 増量投与における薬物動態

5mg/kg 8週間隔投与で効果が維持できない尋常性乾癬、乾癬性関節炎、膿疱性乾癬、乾癬性紅皮症患者の5mg/kg投与8週後の血清中インフリキシマブ濃度（メジアン）は定量限界（0.1μg/mL）未満であったが、これら患者に10mg/kgを投与した場合、10mg/kg投与40週後（8週間隔投与）の血清中インフリキシマブ濃度（メジアン）は1.10μg/mLまで上昇した。



5mg/kg 8週間隔投与で効果が維持できない乾癬患者にレミケード10mg/kgを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=44～51） ↑：レミケード投与

薬物動態パラメータ			増量 0週Cpre	増量 0週C_{1H}	増量 8週Cpre	増量 16週Cpre	増量 40週
投与量	10mg/kg (n=51～44)	平均値±標準偏差 メジアン	1.45±2.23 0.00	230.99±51.77 237.99	2.70±4.05 0.00	3.18±4.30 0.47	3.60±4.56 1.10

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

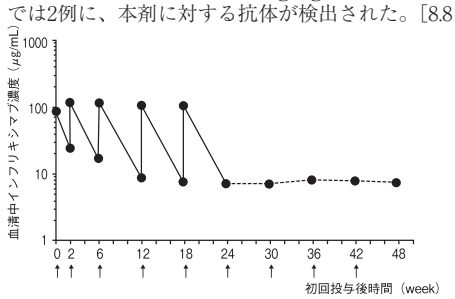
本剤5mg/kg 8週間隔投与で効果が維持できない乾癬患者に対して、本剤6mg/kgを4週間隔で反復投与した場合の推定血清中インフリキシマブ濃度（定常状態の血清中トラフ濃度）[注4)]は、4.63［0.00～37.69］μg/mL（中央値［最小値～最大値］）であった。

注4）増量試験の患者（58例、790点）を対象とした母集団薬物動態解析（NONMEM ver. 7.2.0）に基づく薬物動態パラメータを用いたシミュレーション結果

〈強直性脊椎炎〉

16.1.11 反復投与における薬物動態

本剤5mg/kgを初回、2週後、6週後に投与し、引き続き6週間隔で42週後まで投与したとき、安定した血清中濃度を維持することが観察された。5mg/kgの反復投与を受けた33例では2例に、本剤に対する抗体が検出された。［8.8 参照］



強直性脊椎炎患者にレミケード5mg/kgを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=32～33） ↑：レミケード投与

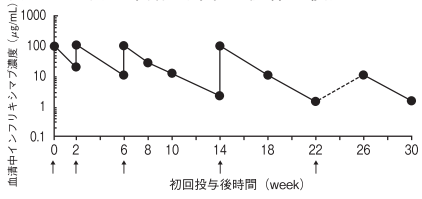
薬物動態パラメータ			0週C_{1H}	24週Cpre	48週
投与量	5mg/kg (n=32～33)	平均値±標準偏差 メジアン	91.76±21.10 86.28	7.40±4.33 7.01	6.96±4.48 7.37

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

〈潰瘍性大腸炎〉

16.1.12 反復投与における薬物動態

本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で22週後まで投与したとき、安定した血清中濃度を維持することが観察された。5mg/kgの反復投与を受けた104例では10例に本剤に対する抗体が検出された。［8.8 参照］



潰瘍性大腸炎患者にレミケード5mg/kgを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=62～104） ↑：レミケード投与

薬物動態パラメータ			0週C_{1H}	6週Cpre	14週Cpre	22週Cpre	30週
投与量	5mg/kg (n=62～104)	平均値±標準偏差 メジアン	95.88±21.50 93.72	11.09±7.19 10.88	3.45±3.98 2.31	2.52±2.73 1.46	2.46±2.73 1.46

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

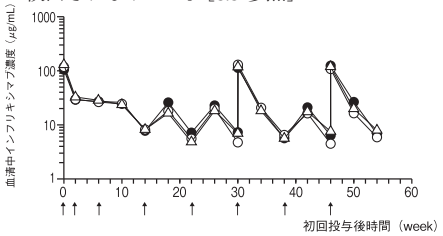
16.1.13 反復投与における薬物動態

ACT1試験において、本剤5mg/kgを初回、2週後、6週後に点滴静脈内投与し、引き続き8週間隔で46週後まで投与したとき、安定した血清中濃度を長期間にわたり維持することが観察された。5mg/kgの反復投与を受けた116例では9例に本剤に対する抗体が検出された（外国人における成績）。［8.8 参照］

〈腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病〉

16.1.14 反復投与における薬物動態

本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週後まで反復投与したとき、病型別に差は認められず、安定した血清中濃度を維持することが観察された。5mg/kgの反復投与を受けた18例において本剤に対する抗体は検出されなかった。［8.8 参照］



腸管型、神経型及び血管型ベーチェット病患者にレミケード5mg/kgを複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン）
↑：レミケード投与
－●－：腸管型ベーチェット病（n=7～11）
－△－：神経型ベーチェット病（n=2又は3）
－○－：血管型ベーチェット病（n=3又は4）

・腸管型ベーチェット病

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre	54週
投与量	5mg/kg (n=8～11)	平均値±標準偏差 メジアン	114.36±27.22 104.55	8.59±4.53 7.78	6.72±3.98 7.30	6.51±3.96 6.77

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

・神経型ベーチェット病

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre (n=2)	54週 (n=2)
投与量	5mg/kg (n=2～3)	平均値±標準偏差 メジアン	116.05±29.09 130.00	9.45±4.09 8.40	6.99 6.99	7.95 7.95

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

・血管型ベーチェット病

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre	54週
投与量	5mg/kg (n=4)	平均値±標準偏差 メジアン	127.09±38.00 117.69	8.86±3.27 8.18	4.95±1.43 4.73	5.62±1.38 5.90

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

16.1.15 増量投与における薬物動態

本剤5mg/kg 8週間隔投与で効果が維持できない腸管型ベーチェット病患者3例に本剤10mg/kgを投与したときの8週後の血清中濃度は、増量前と比較して増加した。

10mg/kgの投与を受けた3例において本剤に対する抗体は検出されなかった。［8.8 参照］

薬物動態パラメータ※			0週Cpre	0週C_{1H}	8週Cpre	8週C_{1H} (n=1)	16週 (n=1)
投与量	10mg/kg (n=1～3)	平均値±標準偏差 メジアン	4.38±3.41 4.39	209.69±51.45 190.57	11.51±6.54 9.77	170.77 -	5.06 -

C_{1H}：投与終了1時間後値、Cpre：投与前値 （μg/mL）

※：10mg/kg初回投与時を0週として集計した。

〈川崎病の急性期〉

16.1.16 単回投与における薬物動態

本剤5mg/kgを単回静脈内投与したときの最高血中濃度（Cmax）は69.80±9.26 μg/mL（平均値±標準偏差）、69.73 μg/mL（中央値）、消失半減期は179.3±71.2時間（平均値±標準偏差）、183.8時間（中央値）であった。本剤投与56日後には16例中11例の血清中インフリキシマブ濃度が定量下限値（0.1 μg/mL）未満であった。5mg/kgの単回投与を受けた16例では7例に本剤に対する抗体が検出された。［8.8 参照］

16.3 分布

ヒトTNFαトランスジェニックマウス及び同系統野生型マウスに、^{35}S標識体インフリキシマブ約10mg/kgを静脈内投与したときの臓器・組織内放射能濃度はいずれも心臓、肺、脾臓に高く、腎臓、肝臓、前肢及び後肢に中程度、消化管では比較的低かった。

16.4 代謝

ヒトTNFαトランスジェニックマウスに^{35}S標識体インフリキシマブ約10mg/kgを静脈内投与したところ、血清中には主として未変化体が検出され、代謝物は検出されなかった。また、ヒトIgG$_1$と同様に細網内皮系細胞等により体内で分解再吸収されるものと推測される。

16.5 排泄

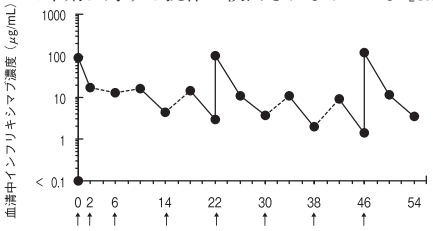
ヒトTNFαトランスジェニックマウスに、^{35}S標識体インフリキシマブ約10mg/kgを静脈内投与したところ、投与14日目までの尿及び糞中へは投与放射能量のそれぞれ11.5%及び12.2%が排泄され、総排泄率は23.7%であった。

16.6 特定の背景を有する患者

16.6.1 小児

〈クローン病〉

(1) 本剤を5mg/kgの用量で3回（0、2、6週）持続静脈内投与後、10週評価時に効果が認められた患者を対象に14週以降8週間隔で投与した時の薬物動態を検討した。8週間隔投与例の投与前の血清中インフリキシマブ濃度（メジアン）は維持された。5mg/kgの反復投与を受けた14例において本剤に対する抗体は検出されなかった。[8.8 参照]



小児クローン病患者にレミケード５mg/kg を複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=８～14，0，22，46週は投与前および投与終了１時間後も表示↑：レミケード投与）

薬物動態パラメータ			0週C_{1H}	14週Cpre	30週Cpre	54週
投与量	5mg/kg（n＝8～14）	平均値±標準偏差 メジアン	91.19±10.60 91.48	4.71±3.36 4.54	4.28±3.32 3.75	4.19±3.69 3.62

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

(2) 増量投与における薬物動態

本剤5mg/kg 8週間隔投与で効果が維持できない患者5例に本剤10mg/kgを投与したときの8週後の血清中濃度は、増量前と比較して増加した。10mg/kgの投与を受けた5例において本剤に対する抗体は検出されなかった。[8.8 参照]

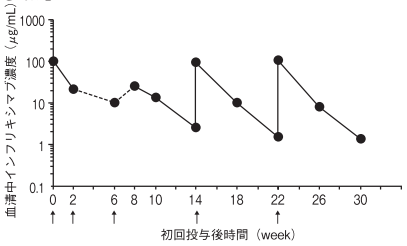
薬物動態パラメータ※			増量 0週Cpre	増量 0週C_{1H}	増量 8週Cpre	増量 16週
投与量	10mg/kg（n＝3～5）	平均値±標準偏差 メジアン	2.85±3.74 0.38	173.87±8.44 173.20	4.57±5.11 1.16	7.82±6.93 9.61

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

※：10mg/kg初回投与時を0週として集計した。

〈潰瘍性大腸炎〉

(3) 本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で22週後まで投与したとき、安定した血清中濃度を維持することが観察された。5mg/kgの反復投与を受けた21例では本剤に対する抗体は検出されなかった。[8.8 参照]



小児の潰瘍性大腸炎の被験者にレミケード５mg/kg を複数回持続静脈内投与した時の血清中インフリキシマブ濃度推移（メジアン，n=14～21）↑：レミケード投与

薬物動態パラメータ			0週C_{1H}	6週Cpre	14週Cpre	22週Cpre	30週
投与量	5mg/kg（n=14～21）	平均値±標準偏差 メジアン	96.18±15.65 97.17	12.34±7.51 10.35	3.30±3.03 2.58	2.68±3.02 1.54	2.74±3.52 1.34

C_{1H}：投与終了1時間後値、Cpre：投与前値　（μg/mL）

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈クローン病〉

17.1.1 国内第Ⅱ相試験（単回投与）

活動期クローン病患者25例を対象とし、本剤1、3、5、10mg/kgを単回投与した。本剤5mg/kgを投与した群のうち、IOIBD指標（投与4週後の値が投与前より2点以上減少もしくは1点以下）では5例中4例、CDAI指標（投与4週後の値が投与前より70ポイント以上減少）では4例中3例が有効であった[2)]。

副作用発現頻度（臨床検査値異常変動は除く）は、本剤5mg/kg投与群で71.4%（5/7例）であった。主な副作用は、眠気42.9%（3/7例）であった。

17.1.2 国内第Ⅲ相試験（維持投与）

本剤5mg/kgを初回、2週後、6週後に投与し10週までに改善（CDAI値が25%以上かつ70ポイント以上の減少）を認めた中等から重度のクローン病患者57例に6週以降は8週間隔で46週まで投与し、効果が消失した場合はそれ以降4週間隔で50週まで投与した。54週後の改善率は82.5%（47/57例）、寛解率（CDAI値が150未満）は61.4%であった（4週間隔投与を行った症例も含む）。なお、4週移行例の最終評価時の改善率は83.3%（15/18例）、寛解率は55.6%（10/18例）であった。

副作用発現頻度は、89.1%（57/64例）であった。主な副作用は、DNA抗体陽性53.1%（34/64例）であった。

17.1.3 国内第Ⅲ相試験（増量投与）

本剤5mg/kg 8週間隔投与では効果が維持できないクローン病患者39例を対象とし、本剤10mg/kg 8週間隔で32週まで投与した。増量8週時点における10mg/kg投与前からのCDAI値の減少量（中央値及び平均値±標準偏差）は95.0及び103.5±87.2（33例）であり、増量40週時点では95.0及び109.7±98.8（26例）であった。

副作用発現頻度は、本剤5mg/kg 8週間隔投与群で91.5%（65/71例）及び本剤10mg/kg 8週間隔投与群で53.8%（21/39例）であった。主な副作用は、5mg/kg群でDNA抗体陽性25.4%（18/71例）、鼻咽頭炎22.5%（16/71例）、10mg/kg群で鼻咽頭炎10.3%（4/39例）、DNA抗体陽性10.3%（4/39例）であった。

17.1.4 国内試験（増量投与含む）（小児）

本剤5mg/kgを初回、2週後、6週後に投与し10週までに改善（PCDAIが15ポイント以上減少、かつ30以下）を認めた中等症から重症の小児のクローン病患者14例に6週以降は8週間隔で46週まで投与し、効果が減弱した場合はそれ以降10mg/kgを8週間隔で46週まで投与した。54週後の改善率は91.7%（11/12例）、寛解率（PCDAI値が10以下）は75.0%（9/12例）であった（10mg/kg 8週間隔投与の増量投与を行った症例も含む）。本剤5mg/kg 8週間隔で効果が減弱した5例において、本剤10mg/kg 8週間隔で投与したとき、増量8週後の寛解率は60.0%（3/5例）であった。

副作用発現頻度は、64.3%（9/14例）であった。主な副作用は、二本鎖DNA抗体陽性50.0%（7/14例）であった。

〈中等度から重度の活動期にあるクローン病患者〉

17.1.5 海外第Ⅱ/Ⅲ相試験（単回投与）

既存治療で効果不十分な中等度から重度の活動期にあるクローン病患者に、プラセボ及び本剤5mg/kgを単回投与した。その結果、有効率（投与4週後におけるCDAI値が投与前より70ポイント以上減少）はプラセボ群17%（4/24例）に対して、5mg/kg群では81%（22/27例）であり、有意差が認められた[3)]。

副作用発現頻度は、本剤投与群で44.4%（12/27例）及びプラセボ群で24.0%（6/25例）であった。主な副作用は、本剤投与群でめまい7.4%（2/27例）、疲労感7.4%（2/27例）であった。

17.1.6 海外第Ⅲ相試験（維持投与）（ACCENT Ⅰ試験）

本剤5mg/kgを単回投与し、2週に改善（CDAI値が25%以上かつ70ポイント以上減少）が認められた活動期クローン病患者に、その後2、6週、以降は8週間隔で46週までプラセボ又は本剤5mg/kg又は10mg/kgを投与した。その結果、初回投与後に認められた効果が消失するまでの期間は本剤維持群で有意に長く（p＝0.002）、その期間はプラセボ維持群19週に対して、5mg/kg、10mg/kg維持群ではそれぞれ38週（p＝0.002）、54週以上（p＜0.001）であった[4)]。

副作用発現頻度は、本剤5mg/kg維持群で65.3%（126/193例）、本剤10mg/kg維持群で58.9%（113/192例）、プラセボ維持群で53.2%（100/188例）であった。主な副作用は、5mg/kg群で頭痛14.0%（27/193例）、不眠症10.9%（21/193例）、10mg/kg群で頭痛16.1%（31/192例）、咳嗽10.4%（20/192例）であった。

〈外瘻を有するクローン病患者〉

17.1.7 海外第Ⅲ相試験（3回投与）

既存治療で効果不十分な外瘻を有するクローン病患者に、プラセボ及び本剤5mg/kgを3回（初回、2週後、6週後）投与した。その結果、有効率（連続した2回の観察時に半数以上の瘻孔が閉鎖）はプラセボ群26%（8/31例）に対して、5mg/kg群では68%（21/31例）であり、有意差が認められた[5)]。

副作用発現頻度は、本剤5mg/kg投与群で48.4%（15/31例）、本剤10mg/kg投与群で53.1%（17/32例）、プラセボ群で45.2%（14/31例）であった。主な副作用は、5mg/kg群で頭痛16.1%（5/31例）、10mg/kg群で疲労感12.5%（4/32例）であった。

17.1.8 海外第Ⅲ相試験（維持投与）（ACCENTⅡ試験）

本剤5mg/kgを初回、2週後、6週後に投与し、10週、14週で改善（半数以上の瘻孔が閉鎖）が認められた外瘻を有するクローン病患者に、その後8週間隔で46週までプラセボ又は本剤5mg/kgを投与した。その結果、14週以降の効果消失までの期間（中央値）はプラセボ維持群14週間に対して、5mg/kg維持群は40週間を超え、5mg/kg維持群ではプラセボ維持群と比較して有意に長く効果を維持できることが示された（p<0.001）[6]。

副作用発現頻度は、本剤5mg/kg維持群で47.1%（65/138例）及びプラセボ維持群で60.4%（87/144例）であった。主な副作用は、5mg/kg群で頭痛8.0%（11/138例）、疲労7.2%（10/138例）、悪心6.5%（9/138例）であった。

〈関節リウマチ〉

17.1.9 国内第Ⅱ/Ⅲ相試験

メトトレキサートに効果不十分な関節リウマチ患者を対象とし、メトトレキサート併用下（6mg/週以上）で、プラセボ及び本剤3mg/kgを初回、2週後、6週後に反復投与した（二重盲検比較試験）。その結果、14週後のACR基準20%以上改善率は、プラセボ群23.4%（11/47例）に対して、本剤投与群61.2%（30/49例）であり、有意差が認められた（p<0.001）。

また、この二重盲検比較試験に参加した患者に対して、二重盲検比較試験の用量に関わらず引き続き3mg/kgを8週間隔で4回投与し、初回投与後54週まで評価した（長期投与試験）。その結果、最終投与8週後のACR基準20%以上改善率は53.3%（24/45例）であり、有効性の維持が認められた。

副作用発現頻度（随伴症状）は、本剤3mg/kg投与群で49.0%（24/49例）及びプラセボ群で51.1%（24/47例）であった。主な副作用（随伴症状）は、3mg/kg群で発熱12.2%（6/49例）であった。

17.1.10 国内第Ⅲ相試験（増量試験）

メトトレキサート併用下（6mg/週以上）で本剤3mg/kgを初回、2週後、6週後に投与し、引き続き3mg/kg、6mg/kgあるいは10mg/kgを8週間隔で反復投与した。成績は以下のとおりであった。

(1) 増量による効果：54週後のACR-N改善（平均値±SD）は3mg/kg群（99例）51.3±32.1、6mg/kg群（104例）53.8±34.4、10mg/kg群（104例）58.3±31.3であり、10mg/kg群では3mg/kg群に対して有意差が認められた（p=0.024）。10週後にACR基準20%以上改善を満たさなかった患者の54週後のACR基準20%以上改善率は3mg/kg投与37.5%（9/24例）、6mg/kg投与61.5%（16/26例）、10mg/kg投与61.5%（16/26例）であった。

(2) 関節破壊の進展防止：関節破壊進展を手及び足のX線スコア（Sharp Score）で評価した結果、本剤投与後の1年間のスコア変化は3mg/kg群0.00、6mg/kg群0.48、10mg/kg群0.00（いずれも中央値）であった。

副作用発現頻度は、86.1%（179/208例）であった。主な副作用は、DNA抗体陽性53.8%（112/208例）であった。

17.1.11 海外第Ⅲ相試験（ATTRACT試験）

メトトレキサート製剤に効果不十分な関節リウマチ患者を対象とし、メトトレキサート併用下（12.5mg/週以上）で、プラセボ及び本剤3mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で54週間反復投与した。成績は下記のとおりであった[7]。

(1) 症状の軽減：54週後のACR基準20%以上改善率は、プラセボ投与群（MTX単独群）17.0%（15/88例）に対し、本剤投与群では41.9%（36/86例）であり、有意差が認められた（p<0.001）。

(2) 関節破壊の進展防止：投与前から54週までの関節破壊進展を手及び足のX線スコア（Sharp Score）で評価した結果、プラセボ群が4.00（中央値）悪化したのに対して、本剤投与群は0.50（中央値）であり、有意に関節破壊の進行が抑制された（p<0.001）。

(3) 身体機能障害の改善：投与前から54週までの日常生活動作（ADL）の改善をHAQスコア（活動制限と介護の必要性等を評価する指標）で評価した結果、プラセボ群0.1（中央値）に対して本剤投与群0.3（中央値）で有意差が認められた（p<0.001）。また、健康関連QOL（SF-36）の身体的健康サマリースコアの変化は、プラセボ群0.6（中央値）に対して本剤投与群1.2（中央値）であり、有意差が認められた（p=0.002）。

副作用発現頻度は、本剤投与群で62.5%（55/88例）及びプラセボ群で44.2%（38/86例）であった。主な副作用は、本剤投与群で頭痛14.8%（13/88例）であった。

〈ベーチェット病による難治性網膜ぶどう膜炎〉

17.1.12 国内第Ⅲ相試験

ベーチェット病による難治性網膜ぶどう膜炎患者を対象とし、本剤5mg/kgを初回、2週後、6週後に反復投与した。その結果、14週間あたりの眼発作回数（平均値±SD）は、投与前10.17±10.60回から投与後0.66±0.98回となり、有意に減少した（p<0.001）。また、14週間あたりの眼発作回数は、投与前後において12例中11例で減少し、そのうち7例で消失した。

副作用発現頻度は、100%（12/12例）であった。主な副作用は、DNA抗体陽性58.3%（7/12例）、皮膚炎41.7%（5/12例）であった。

〈乾癬〉

17.1.13 国内第Ⅲ相試験

尋常性乾癬患者と乾癬性関節炎患者（局面型皮疹が体表面積の10%以上、かつPASI（Psoriasis Area and Severity Index）スコアが12以上）を対象とし、プラセボ及び本剤5mg/kgを初回、2週後、6週後に投与した（検証的試験）。その結果、10週後のPASIスコア75%改善率は、プラセボ群0.0%（0/19例）に対して、本剤投与群68.6%（24/35例）であり、有意差が認められた（p<0.001）。

尋常性乾癬患者（局面型皮疹が体表面積の10%以上、かつPASIスコアが12以上）、乾癬性関節炎患者（腫脹関節数及び疼痛関節数が5以上、かつCRPが1.5mg/dL以上又は朝のこわばりが45分以上）、膿疱性乾癬患者及び乾癬性紅皮症患者を対象とし、本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週後まで投与した（長期投与試験）。その結果、最終評価において、尋常性乾癬患者のPASIスコア75%改善率は54.1%（20/37例）、乾癬性関節炎患者のACR基準20%改善率は83.3%（10/12例）、膿疱性乾癬患者と乾癬性紅皮症患者の全般改善度が「消失又は改善」の割合はそれぞれ57.1%（4/7例）、87.5%（7/8例）であった。

副作用発現頻度は、本剤投与群で85.7%（30/35例）及びプラセボ群で36.8%（7/19例）であった。主な副作用は、本剤投与群でDNA抗体陽性68.6%（24/35例）であった。

17.1.14 国内第Ⅲ相試験（増量投与）

本剤5mg/kg 8週間隔投与では効果が維持できない乾癬患者51例（尋常性乾癬患者31例、乾癬性関節炎患者8例、膿疱性乾癬患者7例、乾癬性紅皮症患者5例）を対象とし、本剤10mg/kg 8週間隔で32週まで投与した。PASIスコアは本剤5mg/kg投与前のスコアを基準値とした。増量24週時点におけるPASIスコア75%改善率は尋常性乾癬患者では40.7%（11/27例）、乾癬性関節炎患者では42.9%（3/7例）、膿疱性乾癬患者では33.3%（2/6例）、乾癬性紅皮症患者では40.0%（2/5例）であった。

副作用発現頻度は、74.5%（38/51例）であった。主な副作用は、二本鎖DNA抗体陽性49.0%（25/51例）であった。

17.1.15 海外第Ⅲ相試験（IMPACT2試験）

乾癬性関節炎患者（腫脹関節数及び疼痛関節数が5以上、かつCRPが1.5mg/dL以上又は朝のこわばりが45分以上）を対象とし、プラセボ及び本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週後まで投与した。その結果、14週後のACR基準20%改善率はプラセボ群11.0%（11/100例）に対して、本剤投与群58.0%（58/100例）であり、有意差が認められた（p<0.001）。関節破壊進展を手及び足のX線スコア（Modified Sharp Score）で評価した結果、24週後のスコア変化（平均値±標準偏差）はプラセボ群0.82±2.62に対して、本剤投与群−0.70±2.53であり、有意差が認められた（p<0.001）[8)、9)]。

副作用発現頻度は、本剤投与群で48.2%（92/191例）及びプラセボ群で26.5%（26/98例）であった（22週まではプラセボ、24週以降は本剤を投与した症例を含む）。主な副作用は、本剤投与群で上気道感染11.0%（21/191例）であった。

〈強直性脊椎炎〉

17.1.16 国内第Ⅲ相試験

既存治療で効果不十分な強直性脊椎炎患者を対象とし、本剤5mg/kgを初回、2週後、6週後に投与し、引き続き6週間隔で投与した（非盲検下）。その結果、24週後、48週後のASAS（Assessment in Ankylosing Spondylitis）基準20%以上改善率はそれぞれ97.0%（32/33例）、96.9%（31/32例）であった。

副作用発現頻度は、87.9%（29/33例）であった。主な副作用は、DNA抗体陽性48.5%（16/33例）であった。

17.1.17 海外第Ⅲ相試験（ASSERT試験）

既存治療で効果不十分な強直性脊椎炎患者を対象とし、プラセボ及び本剤5mg/kgを初回、2週後、6週後に投与し、引き続き6週間隔で投与した。その結果、24週後のASAS基準20%以上改善率はプラセボ群19.2%（15/78例）に対し、本剤投与群では61.2%（123/201例）であり、有意差が認められた（p<0.001）[10)]。

副作用発現頻度は、本剤投与群で64.9%（131/202例）及びプラセボ群で48.0%（36/75例）であった。主な副作用は、本剤投与群で頭痛7.9%（16/202例）であった。

〈潰瘍性大腸炎〉

17.1.18 国内第Ⅲ相試験

既存治療（ステロイド、アザチオプリン等）で効果不十分な潰瘍性大腸炎患者208例を対象とし、プラセボ及び本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で22週後まで投与し、30週後まで有効性を評価した。その結果、主要有効性評価項目である8週後のMayoスコア改善率は、プラセボ群35.6%（37/104例）に対し、本剤投与群54.8%（57/104例）であり、本剤は有意に高い改善率を示した（p＝0.005）。

副作用発現頻度は、本剤投与群で73.1%（76/104例）及びプラセボ群で59.6%（62/104例）であった。主な副作用は、本剤投与群でDNA抗体陽性51.9%（54/104例）であった。

17.1.19 国内小児試験

既存治療（ステロイド、アザチオプリン等）で効果不十分な小児の潰瘍性大腸炎患者21例を対象とし、本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で22週後まで投与し、30週後まで有効性を評価した。その結果、CAIスコア寛解率は、投与2週で60.0%（12/20名）となり、投与6、8週共に80.0%（16/20名）と増加し、投与10～30週までの間では64.3～87.5%で推移した。PUCAIスコア寛解率は、投与2週で35.0%（7/20名）となり、投与6、8週共に40.0%（8/20名）と増加し、その後、投与10～30週までの間では28.6～42.9%で推移した。また、Mayoスコアの改善率及び寛解率は、投与30週でそれぞれ42.9%（3/7例）、14.3%（1/7例）であった。

副作用発現頻度は、71.4%（15/21例）であった。主な副作用は、二本鎖DNA抗体陽性57.1%（12/21例）であった。

17.1.20 海外第Ⅲ相試験（ACT1試験）

既存治療（ステロイド、アザチオプリン等）で効果不十分な潰瘍性大腸炎患者242例に対し、プラセボ及び本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週まで投与し、54週後まで有効性を評価した。その結果、主要有効性評価項目である8週後のMayoスコア改善率は、プラセボ群37.2%（45/121例）に対し、本剤投与群69.4%（84/121例）であり、本剤は有意に高い改善率を示した（p＜0.001）[11]。

副作用発現頻度は、本剤投与群で48.8%（59/121例）及びプラセボ群で42.1%（51/121例）であった。主な副作用は、本剤投与群で頭痛9.9%（12/121例）であった。

〈腸管型ベーチェット病、神経型ベーチェット病、血管型ベーチェット病〉

17.1.21 国内第Ⅲ相試験

既存治療で効果不十分な腸管型、神経型及び血管型ベーチェット病患者を対象とし、本剤5mg/kgを初回、2週後、6週後に投与し、引き続き8週間隔で46週まで投与した。その結果、腸管型ベーチェット病患者での投与30週後の著効例の割合（内視鏡検査で潰瘍の治癒又は瘢痕化を確認でき、臨床症状が消失し、完全寛解となった患者の割合）は54.5%（6/11例）であった。神経型ベーチェット病患者での投与30週後の著効例の割合（急性型：頭部MRI画像検査で高信号域の消失及び髄液中の細胞数及びIL-6濃度が投与前よりも低下し、神経症状が消失した患者の割合、慢性進行型：頭部MRI画像検査で脳幹部の更なる萎縮がなく、髄液中のIL-6濃度が投与前よりも低下し、神経症状の悪化がない患者の割合）は33.3%（1/3例）であった。血管型ベーチェット病患者での投与30週後の著効例の割合（PET/CTなどの画像検査結果及び臨床症状が投与前と悪化せず、CRP及びESRが投与前と比較して低下した患者の割合）は100.0%（4/4例）であった。

副作用発現頻度は、66.7%（12/18例）であった。主な副作用は、二本鎖DNA抗体陽性44.4%（8/18例）であった。

17.1.22 国内第Ⅲ相試験（増量投与）

本剤5mg/kg 8週間隔で効果が維持できない腸管型ベーチェット病患者3例において、本剤10mg/kg 8週間隔で投与したとき、臨床症状や炎症マーカー等の改善傾向が認められた。

なお、3例に副作用は認められなかった。

〈川崎病の急性期〉

17.1.23 国内第Ⅲ相試験

初回の免疫グロブリン療法で効果不十分な川崎病患者31例に対し、ポリエチレングリコール処理人免疫グロブリン（VGIH）2g/kg及び本剤5mg/kgを単回投与し、有効性を評価した。主要有効性評価項目である治験薬投与開始48時間以内の解熱率の点推定値（95%信頼区間）は、本剤投与群76.7%（56.6～96.7%）、VGIH群37.0%（11.9～62.1%）であった。また、冠動脈病変発現率はVGIH群20.0%（3/15例）に対し、本剤投与群6.3%（1/16例）であった。

副作用発現頻度は、本剤投与群で68.8%（11/16例）及びVGIH投与群で66.7%（10/15例）であった。主な副作用は、本剤投与群で二本鎖DNA抗体陽性68.8%（11/16例）であった。

18. 薬効薬理

18.1 作用機序

インフリキシマブはクローン病や関節リウマチの病態形成に密接に関与しているTNF α の作用を阻害する。その機序は可溶性TNF α の生物活性を中和するとともに、膜結合型TNF α 発現細胞をCDC（補体依存性細胞傷害）あるいはADCC（抗体依存性細胞媒介型細胞傷害）により傷害すること、ならびに受容体に結合したTNF α を解離させることによりTNF α の作用を阻害すると考えられている。

18.2 可溶性TNF α 結合作用

可溶性TNF α への結合定数は1.04×10^{10} M^{-1}であった[12]（in vitro）。

18.3 IL-6産生抑制作用

TNF α 刺激による線維芽細胞からのIL-6産生を抑制した[13]（in vitro）。

18.4 膜結合型TNF α 発現細胞に対する傷害作用

ヒトIgG_1のFc領域を有することから、CDC及びADCCにより膜結合型TNF α を発現するTNF α 産生細胞を傷害した[12]（in vitro）。

18.5 受容体結合TNF α 解離作用

TNF α 受容体に結合したTNF α とも結合し、TNF α を受容体から解離させ、接着分子（ICAM-1、VCAM-1）の発現を抑制した（in vitro）。

18.6 TNF α 生物活性に対する中和作用

ヒトTNF α トランスジェニックマウスの死亡率軽減作用が認められた[13]。

19. 有効成分に関する理化学的知見

一般名：インフリキシマブ（遺伝子組換え）［infliximab（genetical recombination）］

分子量：約149,000

本　質：ヒトIgG_1定常領域及びTNF α 特異的なマウス可変領域を有するモノクローナル抗体で、1,328個のアミノ酸残基からなる糖蛋白質。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

100mg［1バイアル（20mL容器）］

23. 主要文献

1）Westhovens R, et al.:Arthritis Rheum. 2006;54（4）:1075-1086
2）Asakura H, et al.:J Gastroenterol Hepatol. 2001;16（7）:763-769
3）Targan SR, et al.:N Engl J Med. 1997;337（15）:1029-1035
4）Hanauer SB, et al.:Lancet. 2002;359:1541-1549
5）Present DH, et al.:N Engl J Med. 1999;340（18）:1398-1405
6）Sands BE, et al.:N Engl J Med. 2004;350（9）:876-885
7）Lipsky PE, et al.:N Engl J Med. 2000;343（22）:1594-1602
8）Antoni C, et al.:Ann Rheum Dis. 2005;64（8）:1150-1157
9）van der Heijde D, et al.:Arthritis Rheum. 2007;56（8）:2698-2707
10）van der Heijde D, et al.:Arthritis Rheum. 2005;52（2）:582-591
11）Rutgeerts P, et al.:N Engl J Med. 2005;353（23）:2462-2476
12）Scallon BJ, et al.:Cytokine. 1995;7（3）:251-259
13）Siegel SA, et al.:Cytokine. 1995;7（1）:15-25

＊24. 文献請求先及び問い合わせ先

田辺ファーマ株式会社　くすり相談センター
〒541-8505 大阪市中央区道修町3-2-10
電話 0120-753-280

26. 製造販売業者等

＊26.1 製造販売元

田辺ファーマ株式会社
大阪市中央区道修町3-2-10

26.2 製造元

Janssen Biotech, Inc.
ペンシルバニア州（アメリカ）

最新の添付文書を参照すること

**2026年8月改訂（第8版、用量変更、用法変更）
*2026年1月改訂
貯　　法：2～8℃で保存すること
有効期間：36カ月

日本標準商品分類番号
873999

ヒト型抗ヒトIL-12/23p40モノクローナル抗体製剤

生物由来製品
劇薬
処方箋医薬品※

ウステキヌマブ（遺伝子組換え）製剤

ステラーラ®点滴静注130mg

Stelara® Intravenous Infusion
※注意－医師等の処方箋により使用すること

承認番号	22900AMX00514000
販売開始	2017年5月

1. 警告

1.1 本剤はIL-12/23の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。[2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.5参照]

1.2 重篤な感染症
ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。[2.1、8.1、9.1.1、11.1.2参照]

1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。[2.2、8.2、9.1.2、11.1.3参照]

1.4 本剤の治療を開始する前に、適応疾患の既存治療の適用を十分勘案すること。[5.1、5.2参照]

1.5 本剤についての十分な知識と適応疾患の治療の知識・経験をもつ医師が使用すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な感染症の患者［症状を悪化させるおそれがある。］[1.1、1.2、8.1、11.1.2参照]

2.2 活動性結核の患者［症状を悪化させるおそれがある。］[1.3、8.2、11.1.3参照]

2.3 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ステラーラ点滴静注130mg
有効成分	（1バイアル26mL中） ウステキヌマブ（遺伝子組換え）130mg含有
添加剤	精製白糖2210mg、L-ヒスチジン20mg、L-ヒスチジン塩酸塩水和物27mg、ポリソルベート80 10.4mg、L-メチオニン10.4mg、エデト酸ナトリウム水和物0.52mg

本剤はマウスミエローマ（Sp2/0）細胞株を用いて製造される。

3.2 製剤の性状

色・性状	無色～淡黄色の澄明な液
pH	5.7～6.3
浸透圧比	約1（生理食塩液に対する比）

4. 効能又は効果

○中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）
○中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）

5. 効能又は効果に関連する注意

〈クローン病〉

5.1 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4参照]

〈潰瘍性大腸炎〉

5.2 過去の治療において、他の薬物療法（ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4参照]

6. 用法及び用量

〈クローン病/潰瘍性大腸炎〉

成人
通常、成人にはウステキヌマブ（遺伝子組換え）として、導入療法の初回に、以下に示す用量を単回点滴静注する。

患者体重	投与量
55kg以下	260mg
55kgを超える85kg以下	390mg
85kgを超える	520mg

**〈クローン病〉

小児
通常、2歳以上の小児にはウステキヌマブ（遺伝子組換え）として、導入療法の初回に、以下に示す用量を単回点滴静注する。

患者体重	投与量
40kg未満	250mg/m²（体表面積）
40kg以上55kg以下	260mg
55kgを超える85kg以下	390mg
85kgを超える	520mg

7. 用法及び用量に関連する注意

7.1 維持療法については、本剤初回投与の8週後、ウステキヌマブ（遺伝子組換え）皮下投与用製剤の投与を行う。維持療法における用法・用量は、ウステキヌマブ（遺伝子組換え）皮下投与用製剤の電子添文を参照すること。

7.2 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。

8. 重要な基本的注意

8.1 本剤はIL-12/23の作用を選択的に抑制する薬剤であり、感染のリスクを増大させる可能性がある。そのため、本剤の投与に際しては、十分な観察を行い、感染症の発症や増悪に注意すること。感染の徴候又は症状があらわれた場合には、直ちに主治医に連絡するよう患者を指導すること。[1.1、1.2、2.1、9.1.1、11.1.2参照]

8.2 本剤投与に先立って結核に関する十分な問診及び胸部X線検査に加え、インターフェロン-γ遊離試験又はツベルクリン反応検査を行い、適宜胸部CT検査等を行うことにより、結核感染の有無を確認すること。
また、本剤投与中も、胸部X線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、結核を疑う症状（持続する咳、体重減少、発熱等）が発現した場合には速やかに担当医に連絡するよう患者に指導すること。[1.1、1.3、2.2、9.1.2、11.1.3参照]

8.3 本剤はIL-12/23の作用を選択的に抑制する薬剤であり、悪性腫瘍発現の可能性があり、臨床試験において皮膚及び皮膚以外の悪性腫瘍の発現が報告されている。本剤との因果関係は明確ではないが、悪性腫瘍の発現には注意すること。[1.1、9.1.3、15.1.5参照]

8.4 生ワクチン接種に起因する感染症発現の可能性を否定できないので、本剤による治療中は、生ワクチンを接種しないこと。[9.5.2 参照]

8.5 他の生物製剤から変更する場合は感染症の徴候について患者の状態を十分に観察すること。

8.6 本剤投与中又は投与当日に Infusion Reaction（発熱、悪寒、嘔気、嘔吐、頭痛、発疹等）が発現する可能性があるため、患者の状態を十分に観察し、異常が認められた場合には直ちに投与を中止し、適切な処置（抗ヒスタミン薬、解熱鎮痛薬の投与等）を行うこと。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 感染症（重篤な感染症を除く）の患者、感染症が疑われる又は再発性感染症の既往歴のある患者

感染症を悪化又は顕在化させるおそれがある。[1.1、1.2、8.1、11.1.2 参照]

9.1.2 結核の既往歴を有する患者又は結核感染が疑われる患者

(1) 結核の既往歴を有する患者では、結核を活動化させるおそれがある。[1.1、1.3、8.2、11.1.3 参照]

(2) 結核の既往歴を有する場合又は結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。下記のいずれかの患者には、結核等の感染症について診療経験を有する医師と連携の下、原則として本剤の投与開始前に適切な抗結核薬を投与すること。[1.1、1.3、8.2、11.1.3 参照]

・胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
・結核の治療歴（肺外結核を含む）を有する患者
・インターフェロン-γ遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
・結核患者との濃厚接触歴を有する患者

9.1.3 悪性腫瘍の既往歴のある患者、悪性腫瘍を発現し、本剤投与継続を考慮している患者

悪性腫瘍の既往歴のある患者を対象とする試験は実施されていない。[1.1、8.3 参照]

9.1.4 アレルゲン免疫療法を受けた患者

アレルゲン免疫療法を受けた患者における本剤の使用については評価されていないが、本剤はアレルゲン免疫療法に影響を与える可能性がある。特にアナフィラキシーに対するアレルゲン免疫療法を受けている又は過去に受けたことのある患者については注意すること。

9.5 妊婦

9.5.1 妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はカニクイザルにおいて胎児への移行が報告されているが、胚・胎児毒性及び催奇形性は認められていない。

9.5.2 本剤の投与を受けた患者からの出生児に対して生ワクチンを投与する際には注意すること。本剤は胎盤通過性があるとの報告があるため、感染のリスクが高まるおそれがある。[8.4 参照]

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトにおいてごく少量乳汁中へ移行することが報告されている。[1)-3)]

**9.7 小児等

2 歳未満の小児を対象とした臨床試験は実施していない。

9.8 高齢者

感染症等の副作用の発現に留意し、十分な観察を行うこと。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

**11.1.1 アナフィラキシー（頻度不明）

発疹、蕁麻疹、血管性浮腫等があらわれることがある。

11.1.2 重篤な感染症（1%未満）

ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。[1.1、1.2、2.1、8.1、9.1.1 参照]

11.1.3 結核（頻度不明）

結核が発現又は再活性化する可能性がある。[1.1、1.3、2.2、8.2、9.1.2 参照]

11.1.4 間質性肺炎（頻度不明）

咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.2 その他の副作用

	1%以上	1%未満	頻度不明
** 感染症及び寄生虫症	上咽頭炎	上気道感染、外陰腟真菌感染、帯状疱疹、副鼻腔炎	歯肉炎
精神障害			うつ病
神経系障害	頭痛	浮動性めまい	
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛、鼻閉	好酸球性肺炎
胃腸障害	悪心	嘔吐、下痢	
皮膚及び皮下組織障害	そう痒症	発疹、蕁麻疹、ざ瘡、過敏性血管炎	膿疱性乾癬、乾癬性紅皮症
筋骨格系及び結合組織障害		関節痛、筋痛、背部痛	
全身障害及び投与局所様態	疲労	無力症、注射部位反応	

14. 適用上の注意

**14.1 薬剤調製時の注意

〈成人及び体重 40kg 以上の小児〉

14.1.1 患者の体重に基づき投与量及び必要な本剤のバイアルの数を算出する。

14.1.2 日局生理食塩液の 250mL 点滴バッグから、追加する本剤と同量分を抜き取る。

14.1.3 必要なバイアルごとに本剤 26mL を 250mL 点滴バッグに加え、穏やかに混合する。総液量は 250mL とする。

〈体重 40kg 未満の小児〉

14.1.4 患者の体表面積に基づき投与量及び必要な本剤のバイアルの数を算出する。

14.1.5 日局生理食塩液の 100mL 点滴バッグから、追加する本剤と同量分を抜き取る。

14.1.6 患者の体表面積より計算した必要量を 100mL 点滴バッグに加え、穏やかに混合する。総液量は 100mL とする。

14.2 薬剤投与時の注意

14.2.1 投与前に本剤の希釈液を目視で確認すること。不透明粒子や変色又は異物が認められた場合は使用しないこと。

14.2.2 本剤の希釈液を 1 時間以上かけて投与すること。

14.2.3 調製後は 8 時間以内に投与完了すること。

14.2.4 本剤は無菌・パイロジェンフリーで蛋白結合性の低いインラインフィルター（ポアサイズ 0.2μm）を用いて投与すること。

14.2.5 他の薬剤と同じ静注ラインで同時注入はしないこと。

14.2.6 本剤のバイアルは 1 回使い切りである。未使用残液については適切に廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 尋常性乾癬（乾癬性関節炎を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験は、72 週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5 年間までの期間で実施されており、乾癬性関節炎を対象とした海外臨床試験は 24 カ月までの期間で実施されている。また、クローン病及び潰瘍性大腸炎では、それぞれ国際共同臨床試験（本剤単回投与後にウステキヌマブ皮下投与用製剤を反復投与）は、52 週間までの期

間で実施されている。これらの期間を超えたウステキヌマブ製剤の長期投与時の安全性は確立していない。

15.1.2 尋常性乾癬（乾癬性関節炎を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験において、153 例中 10 例（6.5%）が 72 週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び乾癬性関節炎を対象とした海外臨床試験においても、ウステキヌマブ皮下投与用製剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。また、約 1 年間の本剤及びウステキヌマブ皮下投与用製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。

15.1.3 尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。

15.1.4 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。

15.1.5 海外の尋常性乾癬、乾癬性関節炎、クローン病、潰瘍性大腸炎を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、ウステキヌマブ投与群が 0.11/100 人年（1 例/929 人年）、プラセボ投与群が 0.23/100 人年（1 例/434 人年）であった。非黒色腫皮膚癌の発現頻度は、ウステキヌマブ投与群が 0.43/100 人年（4 例/929 人年）、プラセボ投与群が 0.46/100 人年（2 例/433 人年）であった。また、対照及び非対照期間において、6710 名（15205 人年）にウステキヌマブが投与された。その追跡調査中央値は 1.2 年で、尋常性乾癬を対象とした臨床試験では 3.2 年、乾癬性関節炎を対象とした臨床試験では 1.5 年、クローン病を対象とした臨床試験では 0.6 年、潰瘍性大腸炎を対象とした臨床試験では 2.3 年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.50/100 人年（76 例/15205 人年）で、主なものは前立腺癌、黒色腫、結腸直腸癌、乳癌であった。ウステキヌマブ投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.94［95%信頼区間：0.73、1.18］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は 0.46/100 人年（56 例/11545 人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は 3：1 であり一般人口で予測される発現頻度と同様であった。［1.1、8.3 参照］

15.2 非臨床試験に基づく情報

15.2.1 げっ歯類の IL-12 及び IL-23 に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40 の阻害により、悪性腫瘍の増大が報告されている。[4] また、IL-12 及び IL-23 の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている。[5]

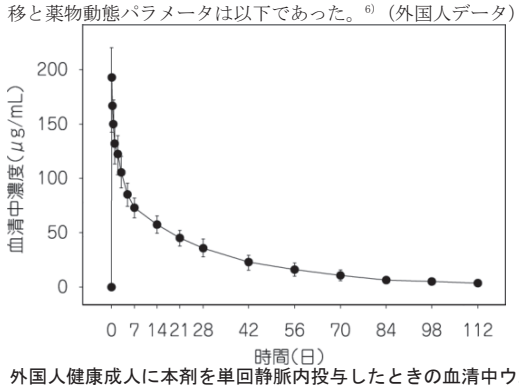
16. 薬物動態

16.1 血中濃度

〈効能共通〉

16.1.1 単回投与

健康成人に本剤 6mg/kg※を単回静脈内投与したときの血中濃度推移と薬物動態パラメータは以下であった。[6]（外国人データ）



外国人健康成人に本剤を単回静脈内投与したときの血清中ウステキヌマブ濃度推移（平均値±標準偏差、69 例）

薬物動態パラメータ（外国人データ）

AUC_{∞} （μg・day/mL）	3132.4 注) (690.2)
$t_{1/2}$ (day)	24.7 注) (6.2)

平均値（標準偏差）、69 例（注）68 例）

※本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg

〈クローン病〉

**16.1.2 単回投与（国際共同臨床試験）

（1）成人

日本人及び外国人のクローン病患者に、用法・用量に従って本剤を単回静脈内投与したとき、血清中ウステキヌマブ濃度は投与 1 時間後に 113（23.7）μg/mL（n=28）及び 126（34.1）μg/mL（n=412）、8 週後に 4.04（2.92）μg/mL（n=15）及び 7.09（4.57）μg/mL（n=292）を示した。[7]［平均値（標準偏差）］

（2）小児

2 歳以上 18 歳未満の日本人及び外国人のクローン病患者に、用法・用量に従って本剤を単回静脈内投与したとき、血清中ウステキヌマブ濃度は投与 1 時間後に 108（29.6）μg/mL（n=98）［日本人の値：103（52.6）μg/mL（n=6）］、8 週後に 4.08（3.54）μg/mL（n=88）［日本人の値：1.78（0.92）μg/mL（n=6）］を示した。[8]［平均値（標準偏差）］

〈潰瘍性大腸炎〉

16.1.3 単回投与（国際共同臨床試験）

日本人及び外国人の潰瘍性大腸炎患者に、用法・用量に従って本剤を単回静脈内投与したとき、血清中ウステキヌマブ濃度は投与 1 時間後に 129（27.4）μg/mL（n=39）及び 126（33.3）μg/mL（n=273）、8 週後に 7.40（4.04）μg/mL（n=36）及び 9.14（5.50）μg/mL（n=224）を示した。[9]［平均値（標準偏差）］

16.4 代謝

ウステキヌマブは、ヒト IgG1 由来の抗体であることから、他の免疫グロブリン[10]と同様に代謝されると推察される。

16.7 薬物相互作用

本剤を承認用法・用量で投与したクローン病患者にカフェイン（CYP1A2 基質）、ワルファリン（CYP2C9 基質）、オメプラゾール（CYP2C19 基質）、デキストロメトルファン（CYP2D6 基質）及びミダゾラム（CYP3A 基質）を併用した際の基質薬の薬物動態パラメータの変化を表に示す。（外国人データ）

薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	n	併用、非併用時の幾何平均値の比 a)（%）（幾何平均値の比の 90%信頼区間（%））	
			22 日目	113 日目
カフェイン（CYP1A2）	C_{max}	15	99.56 (89.22-111.11)	108.40 (97.14-120.98)
	AUC_{∞}	14	102.54 (93.01-113.06)	111.06 (100.73-122.45)
ワルファリン（CYP2C9）	C_{max}	16	96.49 (86.27-107.91)	103.87 (92.87-116.17)
	AUC_{∞}	11	106.60 (95.28-119.27)	102.30 (91.43-114.47)
オメプラゾール（CYP2C19）	C_{max}	15	72.65 (56.82-92.89)	100.68 (78.74-128.73)
	AUC_{∞}	5	95.75 (77.41-118.44)	116.16 (93.91-143.68)
デキストロメトルファン（CYP2D6）	C_{max}	16	90.41 (72.56-112.66)	101.63 (81.56-126.64)
	AUC_{∞}	9	92.26 (70.55-120.65)	107.60 (82.28-140.70)
ミダゾラム（CYP3A）	C_{max}	16	100.95 (87.64-116.27)	88.61 (76.93-102.07)
	AUC_{∞}	16	106.98 (96.16-119.01)	89.92 (80.83-100.04)

a）：8 日目及び 64 日目に本剤を静脈内及び皮下投与（承認用法・用量）、並びに 1 日目、22 日目及び 113 日目に基質薬を投与。併用、非併用時の幾何平均値の比は 22 日目又は 113 日目と 1 日目を比較して算出。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈クローン病〉

17.1.1 第Ⅲ相国際共同臨床試験（CRD3001 試験）

中等症から重症の活動期のクローン病患者（日本人症例 56 例を含む）を対象とし、プラセボ、本剤 130mg 又は体重別用量（6mg/kg）[a] を 0 週目に単回静脈内投与した導入試験を実施した。抗 TNF 薬で効果不十分又は忍容性がなかった患者を対象とした。6 週目に clinical response [注 1)] が得られた被験者の割合は、プラセボ群の

21.5%に対して、本剤 130mg 群で 34.3%、本剤体重別用量（6mg/kg）[a] 群で 33.3%であった。[11]

注 1）Crohn’s Disease Activity Index（CDAI）スコアのベースラインからの 100 ポイント以上の減少（ベースラインの CDAI スコアが 220 ポイント以上 248 ポイント以下の被験者については、CDAI スコアが 150 ポイント未満を達成していた場合、clinical response が得られたとみなした）

投与量	プラセボ	130mg[b]	体重別用量（6mg/kg）[a]
Clinical response rate（6 週目）	21.5%（53/247 例）	34.3%[c]（84/245 例）	33.3%[c]（83/249 例）

a）：本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
b）：国内未承認用量
c）：p<0.01、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定

本剤 130mg 群の副作用発現頻度は、26.0%（64 例/246 例）であった。主要な副作用は、頭痛 7 例（2.8%）、関節痛 5 例（2.0%）、鼻咽頭炎 4 例（1.6%）、発疹 4 例（1.6%）、上気道感染 3 例（1.2%）、そう痒症 3 例（1.2%）、筋痛 3 例（1.2%）であった。
本剤体重別用量（6mg/kg）群の副作用発現頻度は、28.1%（70 例/249 例）であった。主要な副作用は、頭痛 9 例（3.6%）、嘔吐 6 例（2.4%）、悪心 5 例（2.0%）、疲労 5 例（2.0%）、上気道感染 4 例（1.2%）であった。

17.1.2 第Ⅲ相国際共同臨床試験（CRD3002 試験）

中等症から重症の活動期のクローン病患者（日本人症例 26 例を含む）を対象とし、プラセボ、本剤 130mg 又は体重別用量（6mg/kg）[a] を 0 週目に単回静脈内投与した導入試験を実施した。既存治療（コルチコステロイド又は免疫調節剤）で効果不十分であり、かつ抗 TNF 薬による治療歴がないか又は抗 TNF 薬治療歴を有するものの効果不十分又は忍容性がないことが示されていない患者を対象とした。6 週目に clinical response[注 1)] が得られた被験者の割合は、プラセボ群の 28.7%に対して、本剤 130mg 群で 51.7%、本剤体重別用量（6mg/kg）[a] 群で 55.5%であった。[12]

注 1）Crohn’s Disease Activity Index（CDAI）スコアのベースラインからの 100 ポイント以上の減少（ベースラインの CDAI スコアが 220 ポイント以上 248 ポイント以下の被験者については、CDAI スコアが 150 ポイント未満を達成していた場合、clinical response が得られたとみなした）

投与量	プラセボ	130mg[b]	体重別用量（6mg/kg）[a]
Clinical response rate（6 週目）	28.7%（60/209 例）	51.7%[c]（108/209 例）	55.5%[c]（116/209 例）

a）：本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
b）：国内未承認用量
c）：p<0.001、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定

本剤 130mg 群の副作用発現頻度は、13.2%（28 例/212 例）であった。主要な副作用は、頭痛 7 例（3.3%）、悪心 3 例（1.4%）、無力症 3 例（1.4%）、上気道感染 2 例（0.9%）であった。
本剤体重別用量（6mg/kg）群の副作用発現頻度は、12.1%（25 例/207 例）であった。主要な副作用は、頭痛 6 例（2.9%）、上気道感染 3 例（1.4%）、悪心 3 例（1.4%）、鼻咽頭炎 2 例（1.0%）、嘔吐 2 例（1.0%）、疲労 2 例（1.0%）であった。

**17.1.3 第Ⅲ相国際共同臨床試験（CRD3004 試験、小児）（jRCT2031200345）

2 歳以上 18 歳未満の中等症から重症の活動期クローン病患者（日本人症例 6 例を含む）を対象とし、体重別用量[a] を 0 週目に単回静脈内投与した非対照試験を実施した。生物学的製剤（抗 TNF 薬又はベドリズマブ）若しくは既存治療（コルチコステロイド又は免疫調節薬）で効果不十分若しくは忍容性がなかった、又はコルチコステロイドに依存していた患者を対象とした。8 週目に clinical remission[注 1)] が得られた被験者の割合は、46.5%[b]（47 例/101 例）であった。[13]

注 1）PCDAI スコアが 10 以下

a）：本剤の体重別用量：体重 40kg 未満=本剤 250mg/m^2、体重 40kg 以上 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
b）：95%信頼区間 37.1%～56.2%

本剤の 8 週目までの副作用の発現頻度は、7.9%（8 例/101 例）であった。主要な副作用は、嘔吐 2 例（2.0%）、頭痛 2 例（2.0%）であった。

〈潰瘍性大腸炎〉

17.1.4 第Ⅲ相国際共同臨床試験（UC03001 試験）

中等症から重症の活動期の潰瘍性大腸炎患者（日本人症例 107 例を含む）を対象とし、プラセボ、本剤 130mg 又は体重別用量（6mg/kg）[b] を 0 週目に単回静脈内投与した導入試験を実施した。生物学的製剤（抗 TNF 薬又はベドリズマブ）又は既存治療（コルチコステロイド又は免疫調節薬）で効果不十分又は忍容性がなかった患者を対象とした。8 週目に clinical remission[注 1)] が得られた被験者の割合は、プラセボ群の 5.3%に対して、本剤 130mg 群で 15.6%、本剤体重別用量（6mg/kg）[b] 群で 15.5%であった。[9]

注 1）Mayo スコアが 2 以下、かついずれのサブスコアも 1 を超えていない場合

投与量	プラセボ	130mg[c]	体重別用量（6mg/kg）[b]
Clinical remission（8 週目）	5.3%（17/319 例）	15.6%[a]（50/320 例）	15.5%[a]（50/322 例）

a）：p<0.001、対プラセボ群、Cochran-Mantel-Haenszel カイ二乗検定
b）：本剤の体重別用量群（承認用量）：体重 55kg 以下=本剤 260mg、体重 55kg 超 85kg 以下=本剤 390mg、体重 85kg 超=本剤 520mg
c）：国内未承認用量

本剤 130mg 群の副作用発現頻度は、11.2%（36 例/321 例）であった。主要な副作用は、頭痛 7 例（2.2%）、そう痒症 5 例（1.6%）、疲労 3 例（0.9%）、悪心 3 例（0.9%）、浮動性めまい 2 例（0.6%）、無力症 2 例（0.6%）であった。
本剤体重別用量（6mg/kg）群の副作用発現頻度は、14.1%（45 例/320 例）であった。主要な副作用は、上気道感染 5 例（1.6%）、疲労 4 例（1.3%）、そう痒症 3 例（0.9%）、頭痛 3 例（0.9%）、発疹 3 例（0.9%）、ざ瘡 3 例（0.9%）であった。

18. 薬効薬理

18.1 作用機序

In vitro 試験において、本剤はヒトインターロイキン（IL）-12 及び IL-23 を構成する p40 たん白サブユニットに特異的かつ高い親和性で結合し[14]、IL-12 及び IL-23 受容体複合体への結合を阻害した。[15]

18.2 薬理作用

In vitro 試験において、IL-12 及び IL-23 によって活性化されるヘルパーT 細胞及びナチュラルキラー細胞などの免疫担当細胞の細胞内シグナル伝達並びに IFN-γ、IL-17A、IL-17F 及び IL-22 の分泌を抑制した。[16]

19. 有効成分に関する理化学的知見

一般的名称：ウステキヌマブ（遺伝子組換え）
[Ustekinumab (Genetical Recombination)]
分子式：H 鎖　$C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L 鎖　$C_{1034}H_{1596}N_{274}O_{337}S_{6}$
分子量：148,079～149,690
本　質：ウステキヌマブは、ヒトインターロイキン-12 及びインターロイキン-23 の p40 サブユニットに対する遺伝子組換えヒト IgG1 モノクローナル抗体である。
ウステキヌマブは、マウスミエローマ（Sp2/0）細胞により産生される。
ウステキヌマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 分子及び 214 個のアミノ酸残基からなる L 鎖（κ鎖）2 分子で構成される糖タンパク質（分子量：148,079～149,690）である。

20. 取扱い上の注意

20.1 激しく振盪しないこと。
20.2 本剤は遮光保存する必要があるため、使用直前に外箱から取り出すこと。
20.3 凍結しないこと。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

26mL［1 バイアル］

23. 主要文献

1）Klenske E, et al.：J Crohns Colitis. 2019; 13: 267-269
2）Bar-Gil Shitrit A, et al.：Inflamm Bowel Dis. 2021; 27: 742-745
3）Matro R, et al.：Gastroenterology. 2018; 155: 696-704
4）Langowsk JL, et al.：Nature. 2006; 442: 461-465
5）Maeda A, et al.：Cancer Res. 2006; 66: 2962-2969
6）社内資料：健康成人におけるウステキヌマブ製剤の薬物動態比較試験（2017 年 3 月 30 日承認、CTD2.7.1.2）
7）社内資料：クローン病に対する国際共同臨床試験の薬物濃度データの併合結果（2017 年 3 月 30 日承認、CTD2.7.2.2）
**8）社内資料：国際共同第Ⅲ相臨床試験成績（CRD3004）（2026 年 XX 月 XX 日承認、CTD2.7.2.2.1.2）
9）社内資料：国際共同第Ⅲ相臨床試験成績（UC03001 寛解導入試験）（2020 年 3 月 25 日承認、CTD2.7.6.1）
10）Tabrizi MA, et al.：Drug Discov Today. 2006; 11: 81-88
11）社内資料：国際共同第Ⅲ相臨床試験成績（CRD3001）（2017 年 3 月 30 日承認、CTD2.7.6.2）
12）社内資料：国際共同第Ⅲ相臨床試験成績（CRD3002）（2017 年 3 月 30 日承認、CTD2.7.6.3）
**13）社内資料：国際共同第Ⅲ相臨床試験成績（CRD3004）（2026 年 X 月 XX 日承認、CTD2.7.6.3）
14）Luo J, et al.：J Mol Biol. 2010; 402: 797-812
15）社内資料：ウステキヌマブのヒト IL-12 及び IL-23 中和作用機序（2017 年 3 月 30 日承認、CTD2.6.2.1）

16）社内資料：ウステキヌマブのヒト IL-12 及び IL-23 中和作用の機能的効果（2017 年 3 月 30 日承認、CTD2.6.2.1）

*24. 文献請求先及び問い合わせ先

ヤンセンファーマ株式会社 メディカルインフォメーションセンター
〒101-0065 東京都千代田区西神田 3-5-2
フリーダイヤル 0120-183-275
https://www.janssenpro.jp

*26. 製造販売業者等

26.1 製造販売元（輸入）

ヤンセンファーマ株式会社
〒101-0065 東京都千代田区西神田 3-5-2

目次

1.8　添付文書（案）..... 2
1.8.1　効能又は効果（案），用法及び用量（案）並びにその設定根拠..... 2
1.8.1.1　効能又は効果（案）並びに用法及び用量（案）..... 2
1.8.1.2　設定根拠..... 2
1.8.2　使用上の注意（案）及びその設定根拠..... 4

1.8　添付文書（案）

1.8.1　効能又は効果（案），用法及び用量（案）並びにその設定根拠

1.8.1.1　効能又は効果（案）並びに用法及び用量（案）

効能又は効果（案）

中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）

用法及び用量（案）

小児

通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。

患者体重	投与量
40 kg 未満	250 mg/m^2（体表面積）
40 kg 以上 55 kg 以下	260 mg
55 kg を超える 85 kg 以下	390 mg
85 kg を超える	520 mg

1.8.1.2　設定根拠

中等症から重症の活動期クローン病（CD）を有する 2 歳以上 18 歳未満の小児患者を対象とした国際共同第 3 相試験（CNTO1275CRD3004 試験，以下 CRD3004 試験）及び第 1 相試験（CNTO1275CRD1001 試験，以下 CRD1001 試験），並びに中等症から重症の活動期 CD を有する成人患者を対象とした国際共同第 3 相試験（CNTO1275CRD3001 試験，以下 CRD3001 試験，及び CNTO1275CRD3002 試験，以下 CRD3002 試験）の結果に基づき，本剤の用法及び用量（案）を設定した。

CRD3004 試験では，成人 CD で承認された用法及び用量で得られたウステキヌマブの全身曝露量と同程度の曝露量が得られるよう，用法及び用量を選択した【2.7.2.3.4.1】。本剤を体重区分別の用量（40 kg 未満には 250 mg/m^2，40 kg 以上 55 kg 以下には 260 mg， 55 kg 超 85 kg 以下には 390 mg，85 kg 超には 520 mg）を単回静脈内投与した結果，以下の主要評価項目（Week I-8 の clinical remission）及び主要な副次評価項目で，良好な結果が認められた【2.5.4.4.1.1，2.5.4.4.1.2】。

CRD3004 試験の Full Analysis Set（FAS，101 例）での導入期の主要評価項目及び副次評価項目の結果：

- Week I-8 に clinical remission（PCDAI スコアが 10 ポイント以下）が認められた被験者の割合は，46.5%（47 例）であった。

- Week I-8 に corticosteroid-free clinical remission が認められた被験者の割合は 42.6%（43 例）で，Week I-8 の clinical remission と同程度であった。
- Week I-6 に sPCDAI に基づく clinical remission が認められた被験者の割合は，45.5%（46 例）であった。
- Week I-8 に clinical response が認められた被験者の割合は 84.2%（85 例）であった。
- Week I-6 に sPCDAI に基づく clinical response が認められた被験者の割合は，89.1%（90 例）であった。
- 維持期にランダム化された 97 例では，ベースライン時の SES-CD スコアが 3 以上は 94 例（96.9%）であった。このうち，Week M-8 に内視鏡的反応が認められた被験者の割合は 36.2%（34 例）であった。なお，本評価項目は，内視鏡検査を再度実施する前に粘膜治癒のための十分な時間を確保するため，導入期終了 8 週後（Week M-8）に評価した。
- Week M-8 に clinical response が認められた被験者の割合は，85.6%（83/97 例）であった。なお，本評価項目は，遅発レスポンダーも含めた導入期の clinical response を評価するため，導入期終了 8 週後（Week M-8）に評価した。

本剤の静脈内投与による導入療法の有効性は，日本人集団と全体集団でおおむね同様であった【2.5.4.4.1.9】。

また，CRD3004 試験の導入期（Week I-8）での clinical remission，clinical response が認められた被験者の割合，並びに炎症性バイオマーカー（CRP 及び便中カルプロテクチン）の改善は，既承認である成人 CD 患者を対象とした CRD3001 試験及び CRD3002 試験の結果と比べて，良好又は同程度な結果が認められた。Clinical remission 及び clinical response は CRD3004 試験では PCDAI スコア，CRD3001 試験及び CRD3002 試験では CDAI スコアを用いて評価した【2.5.4.6.2】。

- Week I-8/Week 8 に clinical remission が認められた被験者の割合（95% CI）は，CRD3004 試験で 46.5%（37.1%～56.2%，47/101 例），CRD3001 試験/CRD3002 試験（併合）で 29.7%（25.7%～34.0%，136/458 例），CRD3001 試験で 20.9%（16.3%～26.4%），CRD3002 試験で 40.2%（33.8%～47.0%）であり，CRD3001 試験/CRD3002 試験（併合），CRD3001 試験，及び CRD3002 試験と比べて CRD3004 試験で高かった。
- Week I-8/Week 8 に clinical response が認められた被験者の割合（95% CI）は，CRD3004 試験で 84.2%（75.8%～90.0%，85/101 例），CRD3001 試験で 37.8%（32.0%～43.9%，94/249 例），CRD3002 試験で 57.9%（51.1%～64.4%，121/209 例）であり，CRD3001 試験及び CRD3002 試験と比べて CRD3004 試験で高かった。
- CRP 及び便中カルプロテクチンのベースラインからの平均変化量は，小児及び成人 CD 患者を対象とした試験のいずれも減少（改善）を示した。便中カルプロテクチンのベースラインからの変化量の平均値は CRD3001 試験及び CRD3002 試験と比べて CRD3004 試験で大きかった。

CRD3004 試験の導入期での忍容性及び安全性は良好であり，CRD3001 試験及び CRD3002 試験の安全性プロファイルとも一致していた【2.7.4.2.2.1】。また，CRD3004 試験の日本人集団での安全性は，全体集団と同様であった【2.7.4.2.1.9】。

以上より，用法及び用量（案）を以下のとおり設定した。

小児

通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。

患者体重	投与量
40 kg 未満	250 mg/m^2（体表面積）
40 kg 以上 55 kg 以下	260 mg
55 kg を超える 85 kg 以下	390 mg
85 kg を超える	520 mg

1.8.2 使用上の注意（案）及びその設定根拠

使用上の注意（案） 2025 年 6 月改訂（第 5 版）からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠
9. 特定の背景を有する患者に関する注意 **9.7 小児等** 2 歳未満の小児~~等の患者~~を対象とした臨床試験は実施していない。	2 歳未満の小児に対する臨床試験は実施していないことから，設定した。

<table>
<tr><th>使用上の注意（案）
2025 年 6 月改訂（第 5 版）からの変更箇所
（下線：追記箇所，取消線：削除箇所）</th><th>設定根拠</th></tr>
<tr><td>

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 アナフィラキシー（頻度不明）

発疹、蕁麻疹、血管性浮腫等があらわれることがある。

11.1.2 重篤な感染症（1%未満）

ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参照］

11.1.3 結核（頻度不明）

結核が発現又は再活性化する可能性がある。［1.1、1.3、2.2、8.2、9.1.2 参照］

11.1.4 間質性肺炎（頻度不明）

咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.2 その他の副作用

	1%以上	1%未満	頻度不明
感染症及び寄生虫症	~~鼻~~上咽頭炎	上気道感染、外陰腟真菌感染、帯状疱疹、副鼻腔炎	歯肉炎
精神障害			うつ病
神経系障害	頭痛	浮動性めまい	
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛、鼻閉	好酸球性肺炎
胃腸障害	悪心	嘔吐、下痢	
皮膚及び皮下組織障害	そう痒症	発疹、蕁麻疹、ざ瘡、過敏性血管炎	膿疱性乾癬、乾癬性紅皮症
筋骨格系及び結合組織障害		関節痛、筋痛、背部痛	
全身障害及び投与局所様態	疲労	無力症、注射部位反応	

</td><td>

11 既存適応を対象とした臨床試験結果に，CRD3004 試験（導入期）の「関連あり（Related）」と判断された事象を併合解析した結果に基づき，発現頻度を算出した。

11.1.1 令和 7 年 12 月 5 日付『医薬品の電子化された添付文書における「血管性浮腫」の用語につきまして』の連絡に従い，変更した。

11.1.2 「重篤な感染症」は，SOC 「感染症および寄生虫症」のうち，重篤な事象の頻度を記載した。

11.2 MedDRA における PT の変更に伴い，「鼻咽頭炎」は「上咽頭炎」に変更した。

</td></tr>
</table>

使用上の注意（案） 2025 年 6 月改訂（第 5 版）からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠
14. 適用上の注意 **14.1 薬剤調製時の注意** **〈成人及び体重 40kg 以上の小児〉** 14.1.1 患者の体重に基づき投与量及び必要な本剤のバイアルの数を算出する。 14.1.2 日局生理食塩液の 250mL 点滴バッグから、追加する本剤と同量分を抜き取る。 14.1.3 必要なバイアルごとに本剤 26mL を 250mL 点滴バッグに加え、穏やかに混合する。総液量は 250mL とする。 **〈体重 40kg 未満の小児〉** 14.1.4 患者の体表面積に基づき投与量及び必要な本剤のバイアルの数を算出する。 14.1.5 日局生理食塩液の 100mL 点滴バッグから、追加する本剤と同量分を抜き取る。 14.1.6 患者の体表面積より計算した必要量を 100mL 点滴バッグに加え、穏やかに混合する。総液量は 100mL とする。	成人及び体重 40kg 以上の小児と体重 40kg 未満の小児では，薬剤調製方法が異なることから，CCDS に基づき設定した。
上記以外の項目	変更なし

**2026 年 8 月改訂（第 8 版、用量変更、用法変更）最新の添付文書を参照すること
*2026 年 1 月改訂
貯　　法：2～8℃で保存すること
**有効期間：＜45mg シリンジ＞36 カ月、＜45mg バイアル＞24 カ月

日本標準商品分類番号
873999

ヒト型抗ヒト IL-12/23p40 モノクローナル抗体製剤

生物由来製品
劇薬
処方箋医薬品※

ウステキヌマブ（遺伝子組換え）製剤

ステラーラ®皮下注 45 mgシリンジ

**ステラーラ®皮下注 45 mgバイアル（案）

	45 mgシリンジ	**45 mgバイアル
承認番号	22300AMX00422000	
販売開始	2011 年 3 月	

Stelara® Subcutaneous Injection
※注意－医師等の処方箋により使用すること

1. 警告

1.1 本剤は IL-12/23 の作用を選択的に抑制する薬剤であるため、感染のリスクを増大させる可能性がある。また、結核の既往歴を有する患者では結核を活動化させる可能性がある。また、本剤との関連性は明らかではないが、悪性腫瘍の発現が報告されている。本剤が疾病を完治させる薬剤でないことも含め、これらの情報を患者に十分説明し、患者が理解したことを確認した上で、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。また、本剤投与後に副作用が発現した場合には、主治医に連絡するよう患者に注意を与えること。[2.1、8.1-8.3、9.1.1-9.1.3、11.1.2、11.1.3、15.1.6 参照]

1.2 重篤な感染症
ウイルス、細菌及び真菌による重篤な感染症が報告されているため、十分な観察を行うなど感染症の発症に注意すること。[2.1、8.1、9.1.1、11.1.2 参照]

1.3 結核等の感染症について診療経験を有する内科等の医師と十分な連携をとり使用すること。[2.2、8.2、9.1.2、11.1.3 参照]

1.4 本剤の治療を開始する前に、適応疾患の既存治療の適応を十分勘案すること。[5.1、5.2、5.3 参照]

1.5 本剤についての十分な知識と適応疾患の治療の知識・経験をもつ医師が使用すること。

2. 禁忌（次の患者には投与しないこと）

2.1 重篤な感染症の患者［症状を悪化させるおそれがある。］[1.1、1.2、8.1、11.1.2 参照]

2.2 活動性結核の患者［症状を悪化させるおそれがある。］[1.3、8.2、11.1.3 参照]

2.3 本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

**3.1 組成

販売名	ステラーラ皮下注 45mg シリンジ	ステラーラ皮下注 45mg バイアル
有効成分	（1 シリンジ 0.5mL 中）ウステキヌマブ（遺伝子組換え）45mg 含有	（1 バイアル 0.5mL 中）ウステキヌマブ（遺伝子組換え）45mg 含有
添加剤	精製白糖 38mg、L-ヒスチジン 0.5mg、ポリソルベート 80 0.02mg	

本剤はマウスミエローマ（Sp2/0）細胞株を用いて製造される。

**3.2 製剤の性状

販売名	ステラーラ皮下注 45mg シリンジ	ステラーラ皮下注 45mg バイアル
色・性状	無色～淡黄色の澄明又はわずかに混濁した液	
pH	5.7～6.3	
浸透圧比	約 1（生理食塩液に対する比）	

4. 効能又は効果

○既存治療で効果不十分な下記疾患
尋常性乾癬、乾癬性関節炎
○中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）
○中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）

5. 効能又は効果に関連する注意

〈尋常性乾癬及び乾癬性関節炎〉

5.1 以下のいずれかを満たす尋常性乾癬又は乾癬性関節炎患者に投与すること。[1.4 参照]
・紫外線療法を含む既存の全身療法（生物製剤を除く）で十分な効果が得られず、皮疹が体表面積の 10%以上に及ぶ患者。
・難治性の皮疹又は関節症状を有する患者。

〈クローン病〉

5.2 過去の治療において、栄養療法、他の薬物療法（5-アミノサリチル酸製剤、ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

〈潰瘍性大腸炎〉

5.3 過去の治療において、他の薬物療法（ステロイド、アザチオプリン等）等による適切な治療を行っても、疾患に起因する明らかな臨床症状が残る場合に投与すること。[1.4 参照]

6. 用法及び用量

〈尋常性乾癬及び乾癬性関節炎〉

通常、成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し、以降 12 週間隔で投与する。
ただし、効果不十分な場合には 1 回 90mg を投与することができる。

〈クローン病/潰瘍性大腸炎〉

成人
ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に、通常、成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し、以降は 12 週間隔で 90mg を皮下投与する。なお、効果が減弱した場合には、投与間隔を 8 週間に短縮できる。

**〈クローン病〉

小児
ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に、通常、2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として、体重 40kg 未満では 60mg/m^2（体表面積）、体重 40kg 以上では 90mg を皮下投与する。以降は 12 週間隔で体重 40kg 未満では 60mg/m^2（体表面積）、体重 40kg 以上では 90mg を皮下投与する。なお、効果が減弱した場合には、投与間隔を 8 週間に短縮できる。

7. 用法及び用量に関連する注意

〈効能共通〉
7.1 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。
〈尋常性乾癬及び乾癬性関節炎〉
7.2 本剤による治療反応が得られない場合、投与開始から28週以内には増量を含めて治療計画を再考すること。また、増量を行っても十分な治療反応が得られない場合、本剤の投与継続を慎重に再考すること。
〈クローン病/潰瘍性大腸炎〉
7.3 ウステキヌマブ（遺伝子組換え）点滴静注製剤による導入療法の初回投与8週後に、本剤の皮下投与を開始すること。（導入療法における用法・用量は、ウステキヌマブ（遺伝子組換え）の点滴静注製剤の電子添文を参照すること。）
7.4 本剤の8週間隔への投与間隔短縮は、本剤の皮下投与中に効果が減弱した患者に対し、本剤の皮下投与開始から8週以降に行うことができる。本剤の投与間隔を短縮しても16週以内に治療効果が得られない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。
7.5 本剤の皮下投与開始後、本剤の2回目の皮下投与までに治療反応がない場合、投与を継続しても効果が得られない可能性があることから、本剤の投与継続の必要性を検討すること。

8. 重要な基本的注意

8.1 本剤はIL-12/23の作用を選択的に抑制する薬剤であり、感染のリスクを増大させる可能性がある。そのため、本剤の投与に際しては、十分な観察を行い、感染症の発症や増悪に注意すること。感染の徴候又は症状があらわれた場合には、直ちに主治医に連絡するよう患者を指導すること。［1.1、1.2、2.1、9.1.1、11.1.2参照］
8.2 本剤投与に先立って結核に関する十分な問診及び胸部X線検査に加え、インターフェロン-γ遊離試験又はツベルクリン反応検査を行い、適宜胸部CT検査等を行うことにより、結核感染の有無を確認すること。
また、本剤投与中も、胸部X線検査等の適切な検査を定期的に行うなど結核症の発現には十分に注意し、結核を疑う症状（持続する咳、体重減少、発熱等）が発現した場合には速やかに担当医に連絡するよう患者に指導すること。［1.1、1.3、2.2、9.1.2、11.1.3参照］
8.3 本剤はIL-12/23の作用を選択的に抑制する薬剤であり、悪性腫瘍発現の可能性があり、臨床試験において皮膚及び皮膚以外の悪性腫瘍の発現が報告されている。本剤との因果関係は明確ではないが、悪性腫瘍の発現には注意すること。［1.1、9.1.3、15.1.6参照］
8.4 生ワクチン接種に起因する感染症発現の可能性を否定できないので、本剤による治療中は、生ワクチンを接種しないこと。［9.5.2参照］
8.5 他の生物製剤から変更する場合は感染症の徴候について患者の状態を十分に観察すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者
9.1.1 感染症（重篤な感染症を除く）の患者、感染症が疑われる又は再発性感染症の既往歴のある患者
感染症を悪化又は顕在化させるおそれがある。［1.1、1.2、8.1、11.1.2参照］
9.1.2 結核の既往歴を有する患者又は結核感染が疑われる患者
(1) 結核の既往歴を有する患者では、結核を活動化させるおそれがある。［1.1、1.3、8.2、11.1.3参照］
(2) 結核の既往歴を有する場合又は結核感染が疑われる場合には、結核の診療経験がある医師に相談すること。下記のいずれかの患者には、結核等の感染症について診療経験を有する医師と連携の下、原則として本剤の投与開始前に適切な抗結核薬を投与すること。［1.1、1.3、8.2、11.1.3参照］
・胸部画像検査で陳旧性結核に合致するか推定される陰影を有する患者
・結核の治療歴（肺外結核を含む）を有する患者
・インターフェロン-γ遊離試験やツベルクリン反応検査等の検査により、既感染が強く疑われる患者
・結核患者との濃厚接触歴を有する患者
9.1.3 悪性腫瘍の既往歴のある患者、悪性腫瘍を発現し、本剤投与継続を考慮している患者
悪性腫瘍の既往歴のある患者を対象とする試験は実施されていない。［1.1、8.3参照］
9.1.4 アレルゲン免疫療法を受けた患者
アレルゲン免疫療法を受けた患者における本剤の使用については評価されていないが、本剤はアレルゲン免疫療法に影響を与える可能性がある。特にアナフィラキシーに対するアレルゲン免疫療法を受けている又は過去に受けたことのある患者については注意すること。
9.1.5 ラテックス過敏症の既往歴又は可能性のある患者
アレルギー反応を起こすことがあるので注意すること。注射針部分のカバーは、乾燥天然ゴム（ラテックス類縁物質）を含む。
9.5 妊婦
9.5.1 妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤はカニクイザルにおいて胎児への移行が報告されているが、胚・胎児毒性及び催奇形性は認められていない。
9.5.2 本剤の投与を受けた患者からの出生児に対して生ワクチンを投与する際には注意すること。本剤は胎盤通過性があるとの報告があるため、感染のリスクが高まるおそれがある。［8.4参照］
9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。ヒトにおいてごく少量乳汁中へ移行することが報告されている。[1)-3)]
****9.7 小児等**
2歳未満の小児を対象とした臨床試験は実施していない。
9.8 高齢者
感染症等の副作用の発現に留意し、十分な観察を行うこと。一般に生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。
11.1 重大な副作用
****11.1.1 アナフィラキシー**（頻度不明）
発疹、蕁麻疹、血管性浮腫等があらわれることがある。
11.1.2 重篤な感染症（1～5%未満）
ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1参照］
11.1.3 結核（頻度不明）
結核が発現又は再活性化する可能性がある。［1.1、1.3、2.2、8.2、9.1.2参照］
11.1.4 間質性肺炎（頻度不明）
咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部X線、胸部CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。
11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
** 感染症及び寄生虫症	上咽頭炎	上気道感染	外陰腟真菌感染、副鼻腔炎、帯状疱疹、歯肉炎	
精神障害			うつ病	
神経系障害		頭痛、浮動性めまい		
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛	鼻閉	好酸球性肺炎
胃腸障害		悪心、嘔吐	下痢	
皮膚及び皮下組織障害		発疹、そう痒症	ざ瘡、蕁麻疹、過敏性血管炎	膿疱性乾癬、乾癬性紅皮症

	5%以上	1～5%未満	1%未満	頻度不明
筋骨格系及び結合組織障害		関節痛	筋痛、背部痛	
全身障害及び投与局所様態		注射部位反応、疲労	無力症	

14. 適用上の注意

14.1 薬剤投与前の注意

14.1.1 投与前に冷蔵庫から取り出し室温に戻しておくことが望ましい。

14.2 薬剤投与時の注意

14.2.1 皮膚が敏感な部位、皮膚に異常がある部位、乾癬の部位には注射しないこと。

14.2.2 投与部位は、上腕部、腹部、大腿部又は臀部が望ましい。同一箇所へ繰り返し注射することは避けること。

**14.2.3 本剤のバイアルは1回使い切りである。未使用残液については適切に廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 尋常性乾癬（乾癬性関節炎を合併した患者を含む）を対象としたウステキヌマブ皮下投与用製剤の国内臨床試験は、72週間までの期間で実施されている。また、尋常性乾癬を対象としたウステキヌマブ皮下投与用製剤の海外臨床試験は、5年間までの期間で実施されており、乾癬性関節炎を対象とした海外臨床試験は24カ月までの期間で実施されている。また、クローン病及び潰瘍性大腸炎では、それぞれを対象とした本剤の国際共同臨床試験（ウステキヌマブ静注用製剤を単回投与後に本剤を反復投与）は、52週間までの期間で実施されている。これらの期間を超えたウステキヌマブ製剤の長期投与時の安全性は確立していない。

15.1.2 尋常性乾癬（乾癬性関節炎を合併した患者を含む）を対象とした国内臨床試験において、本剤投与により153例中10例（6.5%）が72週目までに抗ウステキヌマブ抗体陽性となり、尋常性乾癬及び乾癬性関節炎を対象とした海外臨床試験においても、本剤投与により 5.2～12.4%の患者が抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する傾向がみられた。また、約1年間の本剤及びウステキヌマブ点滴静注製剤の投与により、クローン病を対象とした国際共同試験において 2.9%、潰瘍性大腸炎を対象とした国際共同試験において 4.6%の患者がそれぞれ抗ウステキヌマブ抗体陽性となった。抗ウステキヌマブ抗体が陽性となった患者では効果が減弱化する可能性がある。

15.1.3 尋常性乾癬を対象とした海外臨床試験において、糖尿病を合併する患者では皮下投与後の血清中ウステキヌマブのトラフ濃度が低く、効果が低い傾向がみられた。

15.1.4 尋常性乾癬に対し免疫抑制剤又は光線療法と併用した場合の安全性及び有効性は確立していない。

15.1.5 本剤との関連性は明らかではないが、海外において可逆性後白質脳症症候群（RPLS）の症例が報告されている。

15.1.6 海外の尋常性乾癬、乾癬性関節炎、クローン病、潰瘍性大腸炎を対象とした臨床試験（第Ⅱ相及び第Ⅲ相試験）において、プラセボ対照期間の非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、本剤投与群が0.11/100人年（1例/929人年）、プラセボ投与群が0.23/100人年（1例/434人年）であった。非黒色腫皮膚癌の発現頻度は、本剤投与群が0.43/100人年（4例/929人年）、プラセボ投与群が0.46/100人年（2例/433人年）であった。また、対照及び非対照期間において、6710名（15205人年）に本剤が投与された。その追跡調査中央値は1.2年で、尋常性乾癬を対象とした臨床試験では3.2年、乾癬性関節炎を対象とした臨床試験では1.5年、クローン病を対象とした臨床試験では0.6年、潰瘍性大腸炎を対象とした臨床試験では2.3年であった。非黒色腫皮膚癌を除く悪性腫瘍の発現頻度は、0.50/100人年（76例/15205人年）で、主なものは前立腺癌、黒色腫、結腸直腸癌、乳癌であった。本剤投与群で報告された悪性腫瘍の発現頻度は、一般人口で予測される発現頻度と同様であった（標準化発生比：0.94［95%信頼区間：0.73、1.18］年齢、性別、人種により補正）。非黒色腫皮膚癌の発現頻度は0.46/100人年（56例/11545人年）であった。皮膚基底細胞癌と皮膚有棘細胞癌の発現比率は3:1であり一般人口で予測される発現頻度と同様であった。［1.1、8.3参照］

15.2 非臨床試験に基づく情報

15.2.1 げっ歯類のIL-12及びIL-23に対して中和活性を示さないため、がん原性試験は実施されていない。げっ歯類のモデルにおいて、IL-12/IL-23p40の阻害により、悪性腫瘍の増大が報告されている。[4] また、IL-12及びIL-23の両方の遺伝子を欠損させたマウスでは、紫外線による皮膚癌の発生時期が早まり、発生頻度も増加することが報告されている。[5]

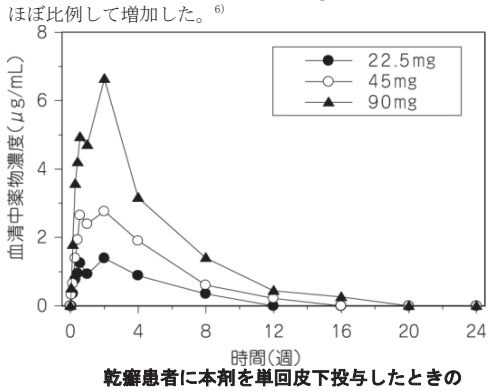
16. 薬物動態

16.1 血中濃度

〈尋常性乾癬及び乾癬性関節炎〉

16.1.1 単回投与

乾癬患者に本剤22.5mg※、45mg及び90mgを単回皮下投与したとき、血清中ウステキヌマブ濃度は投与6.99～10.49日後に最高濃度に達した後、約3週の消失半減期で低下した。血清中ウステキヌマブのC_{max}及びAUC_{∞}は、22.5～90mgの用量範囲において用量にほぼ比例して増加した。[6]



乾癬患者に本剤を単回皮下投与したときの血清中ウステキヌマブ濃度推移（中央値、各6例）

薬物動態パラメータ

用量	22.5mg※	45mg	90mg
C_{max}（μg/mL）	1.44（1.21～1.70）	2.77（2.63～3.38）	9.58（7.23～10.20）
T_{max}（day）	6.99（4.76～12.24）	10.48（4.73～14.00）	10.49（6.98～13.99）
AUC_{∞}（μg・day/mL）	61.3（49.2～75.8）	109.4（96.9～171.9）	242.7（195.7～272.3）

中央値（四分位範囲）、各6例

※本剤の承認用量は1回45/90mgである。

16.1.2 反復投与

乾癬患者に0、4週及びその後12週毎に52週目まで本剤45mg又は90mgを反復皮下投与したとき、血清中ウステキヌマブ濃度は投与開始28週目までに定常状態に達した。本剤45mg又は90mgを反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ0.25～0.31及び0.55～0.76μg/mLであり、用量にほぼ比例して上昇した。[7]

16.1.3 体重の影響

乾癬患者において、体重100kg超の患者に本剤90mgを投与したときの血清中ウステキヌマブのトラフ濃度は体重100kg以下の患者に本剤45mgを投与したときと同程度であった。[8]（外国人データ）

〈クローン病〉

16.1.4 反復投与（国際共同臨床試験）

（1）成人

日本人及び外国人のクローン病患者に、本剤の点滴静注8週後、及びその後8週毎又は12週毎に本剤90mgを皮下投与したとき、血清中ウステキヌマブ濃度は2回目の皮下投与前までに定常状態に達した。日本人及び外国人のクローン病患者に本剤90mgを8週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ1.02～2.14μg/mL（n=7～9）及び1.98～2.26μg/mL（n=74～115）であった。日本人及び外国人のクローン病患者に本剤90mgを12週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ0.37～0.70μg/mL（n=6～7）及び0.62～0.76μg/mL（n=75～103）であった。[9]

（2）小児

2歳以上18歳未満の日本人及び外国人のクローン病患者に、本剤の点滴静注8週後、及びその後、用法・用量に従って、8週毎又は12週毎に本剤を皮下投与したとき、血清中ウステキヌマブ濃度は2回目の皮下投与前までに定常状態に達した。2歳以上18歳未満の日本人及び外国人のクローン病患者に本剤を8週間隔で反

復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値は1.47～1.79μg/mL（n=30～44）であった［日本人の値：0.733～2.63μg/mL（n=1～3）］。2歳以上18歳未満の日本人及び外国人のクローン病患者に本剤を12週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値は0.38～0.63μg/mL（n=27～38）であった［日本人の値：0.00～0.39μg/mL（n=2～3）］。[10]

〈潰瘍性大腸炎〉

16.1.5 反復投与（国際共同臨床試験）

日本人及び外国人の潰瘍性大腸炎患者に、本剤の点滴静注8週後、及びその後8週毎又は12週毎に本剤90mgを皮下投与したとき、血清中ウステキヌマブ濃度は2回目の皮下投与前までに定常状態に達した。日本人及び外国人の潰瘍性大腸炎患者に本剤90mgを8週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ2.46～2.96μg/mL（n=17～18）及び2.69～3.12μg/mL（n=131～148）であった。日本人及び外国人の潰瘍性大腸炎患者に本剤90mgを12週間隔で反復皮下投与したとき、定常状態における血清中ウステキヌマブのトラフ濃度の中央値はそれぞれ0.86～1.03μg/mL（n=17～19）及び0.93～1.23μg/mL（n=122～141）であった。[11]

16.2 吸収

乾癬患者に本剤を単回静脈内投与（0.09、0.27、0.9、4.5mg/kg）又は単回皮下投与（0.27、0.675、1.35、2.7mg/kg）したときの血清中ウステキヌマブ濃度を用いて算出した、ウステキヌマブを皮下投与したときの絶対的バイオアベイラビリティは約57.2%と推定された。（外国人データ）

16.4 代謝

ウステキヌマブは、ヒトIgG1由来の抗体であることから、他の免疫グロブリン[12]と同様に代謝されると推察される。

16.7 薬物相互作用

本剤を承認用法・用量で投与したクローン病患者にカフェイン（CYP1A2基質）、ワルファリン（CYP2C9基質）、オメプラゾール（CYP2C19基質）、デキストロメトルファン（CYP2D6基質）及びミダゾラム（CYP3A基質）を併用した際の基質薬の薬物動態パラメータの変化を表に示す。（外国人データ）

薬物動態パラメータの幾何平均値の比及びその信頼区間

基質薬	薬物動態パラメータ	n	併用、非併用時の幾何平均値の比[a]（%）（幾何平均値の比の90%信頼区間（%））	
			22日目	113日目
カフェイン（CYP1A2）	C_{max}	15	99.56（89.22-111.11）	108.40（97.14-120.98）
	AUC_{∞}	14	102.54（93.01-113.06）	111.06（100.73-122.45）
ワルファリン（CYP2C9）	C_{max}	16	96.49（86.27-107.91）	103.87（92.87-116.17）
	AUC_{∞}	11	106.60（95.28-119.27）	102.30（91.43-114.47）
オメプラゾール（CYP2C19）	C_{max}	15	72.65（56.82-92.89）	100.68（78.74-128.73）
	AUC_{∞}	5	95.75（77.41-118.44）	116.16（93.91-143.68）
デキストロメトルファン（CYP2D6）	C_{max}	16	90.41（72.56-112.66）	101.63（81.56-126.64）
	AUC_{∞}	9	92.26（70.55-120.65）	107.60（82.28-140.70）
ミダゾラム（CYP3A）	C_{max}	16	100.95（87.64-116.27）	88.61（76.93-102.07）
	AUC_{∞}	16	106.98（96.16-119.01）	89.92（80.83-100.04）

a）：8日目及び64日目に本剤を静脈内及び皮下投与（承認用法・用量）、並びに1日目、22日目及び113日目に基質薬を投与。併用、非併用時の幾何平均値の比は22日目又は113日目と1日目を比較して算出。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈尋常性乾癬及び乾癬性関節炎〉

17.1.1 国内臨床試験（第Ⅱ/Ⅲ相試験）

中等症から重症の局面型皮疹を有する尋常性乾癬及び乾癬性関節炎（局面型皮疹の病変が体表面積（BSA）の10%以上、かつPASIスコアが12以上）患者を対象とし、プラセボ、ウステキヌマブ45mg及び90mgを0、4週に投与し、以降12週毎にウステキヌマブを52週まで投与したプラセボ対照二重盲検比較試験を実施した。12週後のPASI[注1)]スコアがベースラインから75%以上改善した患者の割合（以下、PASI75）を下表に示す。12週後の本剤投与群におけるPASI75は、プラセボ群に比べて有意に高かった。その後、緩やかに上昇した後64週目までほぼ一定の値で推移した。[7]

注1）Psoriasis Area and Severity Index

投与量	プラセボ	45mg	90mg
12週後PASI75	6.5%（2/31例）	59.4%[a]（38/64例）	67.7%[a]（42/62例）

a）：p<0.0001、対プラセボ群、Fisherの正確検定

本剤45mg群の副作用発現頻度は、87.5%（56例/64例）であった。主要な副作用は、鼻咽頭炎27例（42.2%）、関節痛6例（9.4%）、頭痛5例（7.8%）、下痢4例（6.3%）、そう痒症2例（3.1%）であった。

本剤90mg群の副作用発現頻度は、87.1%（54例/62例）であった。主要な副作用は、鼻咽頭炎26例（41.9%）、ざ瘡3例（4.8%）、上気道感染2例（3.2%）、蕁麻疹2例（3.2%）、背部痛2例（3.2%）であった。

〈クローン病〉

17.1.2 国際共同臨床試験（第Ⅲ相試験）

中等症から重症の活動期のクローン病患者（日本人症例20例を含む）を対象とした本剤の導入試験から移行した被験者を対象に、プラセボ又は本剤90mg（8週間隔又は12週間隔）を皮下投与した維持試験を実施した。本剤の導入試験で8週目にclinical response[注1)]が得られた被験者における本試験44週目のclinical remission rate[注2)]を下表に示す。44週目にclinical remissionが得られた被験者の割合は、プラセボ群の35.9%に対して、本剤90mgの8週間隔投与群で53.5%、本剤90mgの12週間隔投与群で48.8%であった。[9]

注1）Crohn's Disease Activity Index（CDAI）スコアのベースラインからの100ポイント以上の減少（ベースラインのCDAIスコアが220ポイント以上248ポイント以下の被験者については、CDAIスコアが150ポイント未満を達成していた場合、clinical responseが得られたとみなした）

注2）CDAIスコア<150ポイント

投与量	プラセボ	90mg 8週間隔投与	90mg 12週間隔投与
Clinical remission rate	35.9%（47/131例）	53.5%[a]（68/127例）	48.8%[b]（63/129例）

a）：p<0.01、対プラセボ群、Cochran-Mantel-Haenszelカイ二乗検定

b）：p<0.05、対プラセボ群、Cochran-Mantel-Haenszelカイ二乗検定

本剤90mg 8週間隔投与群の副作用発現頻度は、29.8%（39例/131例）であった。主要な副作用は、上気道感染6例（4.6%）、頭痛5例（3.8%）、鼻咽頭炎4例（3.1%）、外陰腟真菌感染3例（2.3%）、悪心3例（2.3%）であった。

本剤90mg 12週間隔投与群の副作用発現頻度は、25.8%（34例/132例）であった。主な副作用は、頭痛4例（3.0%）、疲労3例（2.3%）、悪心3例（2.3%）、上気道感染2例（1.5%）、鼻咽頭炎2例（1.5%）、発疹2例（1.5%）であった。

****17.1.3 国際共同臨床試験（第Ⅲ相試験：CRD3004試験、小児）（jRCT2031200345）**

2歳以上18歳未満の中等症から重症の活動期クローン病患者（日本人症例6例を含む）を対象に、非盲検の単回静脈内投与による導入療法後に、本剤（8週間隔又は12週間隔）の皮下投与[a)]による維持療法を検討した。維持期44週目にclinical remission[注1)]が得られた被験者の割合は、本剤8週間隔投与群で48.8%[b)]、本剤12週間隔投与群で59.1%[c)]であった。[13]

注1）PCDAIスコアが10以下

投与群	8週間隔投与	12週間隔投与
Clinical remission rate	48.8%[b)]（20/41例）	59.1%[c)]（26/44例）

a）：体重40kg未満=本剤60mg/m²、体重40kg以上=本剤90mg

b）：95%信頼区間 34.3%～63.5%

c）：95%信頼区間 44.4%～72.3%

本剤8週間隔投与群の44週目までの副作用の発現頻度は、2.1%（1例/48例）であった。副作用は頭痛1例（2.1%）であった。本剤12週間隔投与群の44週目までの副作用発現頻度は4.1%（2例/49例）であった。副作用は上咽頭炎1例（2.0%）、上気道感染1例（2.0%）、発疹1例（2.0%）であった。

〈潰瘍性大腸炎〉

17.1.4 国際共同臨床試験（第Ⅲ相試験）

中等症から重症の活動期の潰瘍性大腸炎患者（日本人症例92例を含む）を対象とした本剤の導入試験から移行した被験者を対象に、プラセボ又は本剤90mg（8週間隔又は12週間隔）を皮下投与した維持試験を実施した。44週目にclinical remission[注1)]が得られた被験者の割合は、プラセボ群の24.0%に対して、本剤90mgの8週間隔投与群で43.8%、本剤90mgの12週間隔投与群で38.4%であった。[11]

注1）Mayoスコアが2以下、かついずれのサブスコアも1を超えていない場合

投与量	プラセボ	90mg 8週間隔投与	90mg 12週間隔投与
Clinical remission	24.0%（42/175例）	43.8%[a]（77/176例）	38.4%[b]（66/172例）

a）：p<0.001、対プラセボ群、Cochran-Mantel-Haenszelカイ二乗検定

b）：p<0.01、対プラセボ群、Cochran-Mantel-Haenszelカイ二乗検定

本剤 90mg 8 週間隔投与群の副作用発現頻度は、26.1%（46 例/176 例）であった。主要な副作用は、上気道感染 5 例（2.8%）、発疹 5 例（2.8%）、ざ瘡 3 例（1.7%）、頭痛 3 例（1.7%）、注射部位反応 3 例（1.7%）であった。
本剤 90mg 12 週間隔投与群の副作用発現頻度は、17.4%（30 例/172 例）であった。主な副作用は、疲労 3 例(1.7%)、関節痛 3 例(1.7%)、頭痛 3 例（1.7%）、上気道感染 2 例（1.2%）、発疹 2 例（1.2%）であった。

18. 薬効薬理

18.1 作用機序

In vitro 試験において、本剤はヒトインターロイキン（IL）-12 及び IL-23 を構成する p40 たん白サブユニットに特異的かつ高い親和性で結合し[14]、IL-12 及び IL-23 受容体複合体への結合を阻害した。[15]

18.2 薬理作用

In vitro 試験において、IL-12 及び IL-23 によって活性化されるヘルパーT 細胞及びナチュラルキラー細胞などの免疫担当細胞の細胞内シグナル伝達並びに IFN-γ、IL-17A、IL-17F 及び IL-22 の分泌を抑制した。[16]

19. 有効成分に関する理化学的知見

一般的名称：ウステキヌマブ（遺伝子組換え）
[Ustekinumab (Genetical Recombination)]
分子式：H 鎖　$C_{2207}H_{3410}N_{582}O_{671}S_{17}$
L 鎖　$C_{1034}H_{1596}N_{274}O_{337}S_{6}$
分子量：148,079～149,690
本　質：ウステキヌマブは、ヒトインターロイキン-12 及びインターロイキン-23 の p40 サブユニットに対する遺伝子組換えヒト IgG1 モノクローナル抗体である。
ウステキヌマブは、マウスミエローマ（Sp2/0）細胞により産生される。
ウステキヌマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 分子及び 214 個のアミノ酸残基からなる L 鎖（κ鎖）2 分子で構成される糖タンパク質（分子量：148,079～149,690）である。

20. 取扱い上の注意

20.1 激しく振盪しないこと。
20.2 本剤は遮光保存する必要があるため、使用直前に外箱から取り出すこと。
20.3 凍結しないこと。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

**22. 包装

〈ステラーラ皮下注 45mg シリンジ〉
0.5mL［1 シリンジ］
〈ステラーラ皮下注 45mg バイアル〉
0.5mL［1 バイアル］

23. 主要文献

1) Klenske E, et al.: J Crohns Colitis. 2019; 13: 267-269
2) Bar-Gil Shitrit A, et al.: Inflamm Bowel Dis. 2021; 27: 742-745
3) Matro R, et al.: Gastroenterology. 2018; 155: 696-704
4) Langowsk JL, et al.: Nature. 2006; 442: 461-465
5) Maeda A, et al.: Cancer Res. 2006; 66: 2962-2969
6) 社内資料：国内第Ⅰ相臨床試験成績（JNS009-JPN-01）（2011 年 1 月 21 日承認、CTD2.5.3.2）
7) 社内資料：国内第Ⅱ/Ⅲ相臨床試験成績（JNS009-JPN-02）（2011 年 1 月 21 日承認、CTD2.7.6.7）
8) 社内資料：外国第Ⅲ相臨床試験成績（PHOENIX 1）（2011 年 1 月 21 日承認、CTD2.5.3.3）
9) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3003）（2017 年 3 月 30 日承認、CTD2.7.6.4）
**10) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3004）（2026 年 XX 月 XX 日承認、CTD2.7.2.2.1.2）
11) 社内資料：国際共同第Ⅲ相臨床試験成績（UCO3001 寛解維持試験）（2020 年 3 月 25 日承認、CTD2.7.6.2）
12) Tabrizi MA, et al.:Drug Discov Today. 2006; 11: 81-88
**13) 社内資料：国際共同第Ⅲ相臨床試験成績（CRD3004）（2026 年 X 月 XX 日承認、CTD2.7.6.3）
14) Luo J, et al.：J Mol Biol. 2010; 402: 797-812
15) 社内資料：ウステキヌマブのヒト IL-12 及び IL-23 中和作用機序（2011 年 1 月 21 日承認、CTD2.6.2.1）
16) 社内資料： ウステキヌマブのヒト IL-12 及び IL-23 中和作用の機能的効果（2011 年 1 月 21 日承認、CTD2.6.2.1）

*24. 文献請求先及び問い合わせ先

ヤンセンファーマ株式会社　メディカルインフォメーションセンター
〒101-0065 東京都千代田区西神田 3-5-2
フリーダイヤル 0120-183-275
https://www.janssenpro.jp

*26. 製造販売業者等

26.1 製造販売元（輸入）

ヤンセンファーマ株式会社
〒101-0065 東京都千代田区西神田 3-5-2

目次

1.8　添付文書（案）..... 2
1.8.1　効能又は効果（案），用法及び用量（案）並びにその設定根拠..... 2
1.8.1.1　効能又は効果（案）並びに用法及び用量（案）..... 2
1.8.1.2　設定根拠..... 2
1.8.2　使用上の注意（案）及びその設定根拠..... 4

1.8　添付文書（案）

1.8.1　効能又は効果（案），用法及び用量（案）並びにその設定根拠

1.8.1.1　効能又は効果（案）並びに用法及び用量（案）

効能又は効果（案）

中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る）

用法及び用量（案）

小児

ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，体重 40 kg 未満では 60 mg/m^2（体表面積），体重 40 kg 以上では 90 mg を皮下投与する。以降は 12 週間隔で体重 40 kg 未満では 60 mg/m^2（体表面積），体重 40 kg 以上では 90 mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。

1.8.1.2　設定根拠

中等症から重症の活動期クローン病（CD）を有する 2 歳以上 18 歳未満の小児患者を対象とした国際共同第 3 相試験（CNTO1275CRD3004 試験，以下 CRD3004 試験）及び第 1 相試験（CNTO1275CRD1001 試験，以下 CRD1001 試験），並びに中等症から重症の活動期 CD を有する成人患者を対象とした国際共同第 3 相試験（CNTO1275CRD3003 試験，以下 CRD3003 試験）の結果に基づき，本剤の用法及び用量（案）を設定した。

CRD3004 試験では，導入期（Week I-0 から Week I-8 まで）に clinical response が認められた被験者を対象に，本剤（40 kg 未満では 60 mg/m^2，40 kg 以上では 90 mg）を 8 週間隔（q8w）又は 12 週間隔（q12w）で皮下投与した結果，以下の副次評価項目で，両群ともに良好な結果が認められた【2.5.4.4.1.2】。

CRD3004 試験の Full Clinical Responder Analysis Set［FASCR（Week I-8 で clinical response が認められた被験者），85 例］での維持期の副次評価項目の結果：

- Week M-44 に clinical remission が認められた被験者の割合［95%信頼区間（CI）］は，併合群（q8w 群及び q12w 群の併合）で 54.1%（43.6%～64.3%，46/85 例），q12w 群で 59.1%（44.4%～72.3%，26/44 例），q8w 群で 48.8%（34.3%～63.5%，20/41 例）であった。q8w 群と比べて q12w 群で高かったが，95% CI は q12w 群と q8w 群で重なっていた。
- Week M-44 に clinical response が認められた被験者の割合は，併合群で 60.0%（51/85 例），q12w 群で 63.6%（28/44 例），q8w 群で 56.1%（23/41 例）であった。
- Week M-44 に corticosteroid-free clinical remission が認められた被験者の割合は，併合群で 52.9%（45/85 例），q12w 群で 59.1%（26/44 例），q8w 群で 46.3%（19/41 例）であった。

・ Week I-8 に clinical remission が認められた 47 例のうち，Week M-44 に clinical remission が認められた被験者の割合（95% CI）は，併合群で 68.1%（53.8%～79.6%，32/47 例），q12w 群で 62.5%（42.7%～78.8%，15/24 例），q8w 群で 73.9%（53.5%～87.5%，17/23 例）であった。q8w 群と比べて q12w 群で低かったが，95% CI は，q12w 群と q8w 群で重なっていた。

本剤の皮下投与による維持療法の有効性は，日本人集団と全体集団でおおむね同様であった【2.5.4.4.1.9】。

また，CRD3004 試験の維持期（Week M-44）での clinical remission，clinical response が認められた被験者の割合，並びに炎症性バイオマーカー（CRP 及び便中カルプロテクチン）の改善は，既承認である成人 CD 患者を対象とした CRD3003 試験の結果と比べて，CRD3004 試験で良好又は同程度な結果が認められた。Clinical remission 及び clinical response は CRD3004 試験では PCDAI スコア，CRD3003 試験では CDAI スコアを用いて評価した【2.5.4.6.2.2】。

・ Week M-44/Week 44 で clinical remission が認められた被験者の割合（95% CI）は，CRD3004 試験で 54.1%（43.6%～64.3%，46/85 例），CRD3003 試験で 51.0%（44.9%～57.0%，131/257 例）であり，同程度であった。

・ Week I-8/Week 0 に clinical remission が認められた被験者のうち，Week M-44/Week 44 に clinical remission が認められた被験者の割合（95% CI）は，CRD3004 試験で 68.1%（53.8%～79.6%，32/47 例），CRD3003 試験で 61.5%（53.7%～68.8%，96/156 例）であり，CRD3003 試験と比べて CRD3004 試験で高かったが，95% CI は重なっていた。

・ Week M-44/Week 44 で clinical response が認められた被験者の割合（95% CI）は，CRD3004 試験で 60.0%（49.4%～69.8%，51/85 例），CRD3003 試験で 58.8%（52.7%～64.6%，151/257 例）であり，同程度であった。

・ CRP 及び便中カルプロテクチンのベースラインからの変化量の平均値は，CRD3004 試験及び CRD3003 試験で低下し，改善がみられた。

・ Week M-44/Week 44 に内視鏡的反応が認められた被験者の割合（95% CI）は，CRD3004 試験で 27.7%（19.2%～38.2%，23/83 例），CRD3003 試験で 17.4%（9.1%～30.7%，8/46 例）であり，CRD3003 試験と比べて CRD3004 試験で高かったが，95% CI は重なっていた。

CRD3004 試験の効果減弱が認められた被験者では， q8w 又は q4w への用量調節後に clinical remission 及び clinical response が認められた。

・ 維持期で効果減弱が認められ，ウステキヌマブの血清中トラフ濃度が 1.4 μg/mL 以上であった被験者は，q12w から q8w に用量調節する，又は q8w の投与を継続（見かけ上の用量調節）した。q12w から q8w に用量調節した 2 例全例（100.0%）及び用量調節後 16 週間 q8w を継続投与（見かけ上の用量調節）した 5 例中 3 例（60.0%）で Week M-44 での clinical remission が認められた。なお，維持期で効果減弱が認められた又は早期離脱基準に合致した（Week M-8 までに clinical response が認められなかった），かつ，ウステキヌマブの血清中トラフ濃度が低濃度（1.4 μg/mL 以下）であった被験者は，曝露量最適化サブスタディに移行し，q4w で投与された。用量調節後 16 週時点で，clinical remission 及び clinical response

を認めた被験者はそれぞれ 20 例中 10 例（50.0%）及び 19 例（95.0%）であった。本サブスタディの結果から，効果減弱が認められ，かつウステキヌマブの血清中トラフ濃度が低濃度であった小児 CD 患者に対する q4w への用量調節に一定のベネフィットは示唆されたが，ウステキヌマブの血清中トラフ濃度に基づいた用量調節の判断は本邦の臨床現場では困難であると判断したため，本承認申請では q4w の用量調節は，小児 CD 患者に対する推奨用法及び用量には含めないこととした。

CRD3004 試験の維持期での忍容性及び安全性は良好であり，CRD3003 試験の安全性プロファイルとも一致していた【2.7.4.2.2.2】。また，CRD3004 試験の日本人集団での安全性は，全体集団と同様であった【2.7.4.2.1.9】。

CRD3004 試験の曝露-反応（E-R）解析の結果から，biologic failure（生物学的製剤に一次無効，二次無効又は忍容性がない）の部分集団では，正の E-R 傾向が認められた。これは CRD3003 試験の結果と同様であった【2.5.4.6.2.6】。

また，モデルに基づく E-R 解析の結果では，維持期の定常状態 C_{trough} と Week M-44 に clinical remission が認められた被験者の割合との間の E-R 関係の傾向は，成人及び小児で同様であった【2.7.2.3.3.1】。

小児 CD 患者に推奨する用法及び用量は，CRD3004 試験の結果に加え，成人 CD 患者の臨床試験結果も踏まえて決定している。CRD3004 試験のいずれの投与群（q12w 群，q8w 群）でも良好な有効性及び安全性が認められた。また，CRD3004 試験で効果減弱のため q12w から q8w に用量調節（投与間隔を短縮）した被験者は少数例であったが，有効性が確認された。E-R 解析の結果からも biologic failure の被験者では正の E-R 傾向が認められ，用量調節によるベネフィットが示唆された。これらの結果は，成人 CD 患者を対象とした CRD3003 試験で認められた結果からも支持され，小児 CD 患者の効果減弱例に対しても成人と同様に用量調節（投与間隔を短縮）することによるベネフィットが示唆された。

以上より，用法及び用量（案）を以下のとおり設定した。

小児

ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，体重 40 kg 未満では 60 mg/m^2（体表面積），体重 40 kg 以上では 90 mg を皮下投与する。以降は 12 週間隔で体重 40 kg 未満では 60 mg/m^2（体表面積），体重 40 kg 以上では 90 mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。

1.8.2 使用上の注意（案）及びその設定根拠

使用上の注意（案） 2025 年 6 月改訂（第 5 版）からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠
9. 特定の背景を有する患者に関する注意 **9.7 小児等** 2 歳未満の小児~~等の患者~~を対象とした臨床試験は実施していない。	2 歳未満の小児に対する臨床試験は実施していないことから，設定した。

使用上の注意（案） 2025 年 6 月改訂（第 5 版）からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 アナフィラキシー（頻度不明）

発疹、蕁麻疹、血管性浮腫等があらわれることがある。

11.1.2 重篤な感染症（1～5%未満）

ウイルス、細菌あるいは真菌による重篤な感染症（蜂巣炎、憩室炎、骨髄炎、胃腸炎、肺炎及び尿路感染等）があらわれることがある。重篤な感染症が発現した場合には、感染が回復するまで本剤の投与をしないこと。［1.1、1.2、2.1、8.1、9.1.1 参照］

11.1.3 結核（頻度不明）

結核が発現又は再活性化する可能性がある。［1.1、1.3、2.2、8.2、9.1.2 参照］

11.1.4 間質性肺炎（頻度不明）

咳嗽、呼吸困難、発熱、肺音の異常（捻髪音）等が認められた場合には、速やかに胸部 X 線、胸部 CT、血清マーカー等の検査を実施すること。間質性肺炎が疑われた場合には投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。

11.2 その他の副作用

	5%以上	1～5%未満	1%未満	頻度不明
感染症及び寄生虫症	~~鼻~~上咽頭炎	上気道感染	外陰腟真菌感染、副鼻腔炎、帯状疱疹、歯肉炎	
精神障害			うつ病	
神経系障害		頭痛、浮動性めまい		
呼吸器、胸郭及び縦隔障害		咽喉頭疼痛	鼻閉	好酸球性肺炎
胃腸障害		悪心、嘔吐	下痢	
皮膚及び皮下組織障害		発疹、そう痒症	ざ瘡、蕁麻疹、過敏性血管炎	膿疱性乾癬、乾癬性紅皮症
筋骨格系及び結合組織障害		関節痛	筋痛、背部痛	
全身障害及び投与局所様態		注射部位反応、疲労	無力症	

11 既存適応を対象とした臨床試験結果に，CRD3004 試験（導入期，維持期）の「関連あり（Related）」と判断された事象を併合解析した結果に基づき，発現頻度を算出した。

11.1.1 令和 7 年 12 月 5 日付『医薬品の電子化された添付文書における「血管性浮腫」の用語につきまして』の連絡に従い，変更した。

11.1.2 「重篤な感染症」は，SOC 「感染症および寄生虫症」のうち，重篤な事象の頻度を記載した。

11.2 MedDRA における PT の変更に伴い，「鼻咽頭炎」は「上咽頭炎」に変更した。

使用上の注意（案） 2025 年 6 月改訂（第 5 版）からの変更箇所 （下線：追記箇所，取消線：削除箇所）	設定根拠
14. 適用上の注意 14.1 ＜略＞ 14.2 薬剤投与時の注意 14.2.1 皮膚が敏感な部位、皮膚に異常がある部位、乾癬の部位には注射しないこと。 14.2.2 投与部位は、上腕部、腹部、大腿部又は臀部が望ましい。同一箇所へ繰り返し注射することは避けること。 14.2.3 本剤のバイアルは 1 回使い切りである。未使用残液については適切に廃棄すること。	14.2.3 本剤のバイアルにおける注意すべき点について設定した。
上記以外の項目	変更なし

1.9　一般的名称に係る文書

平成 23 年 1 月 21 日承認時資料第 1 部 1.9 参照。

1.10 毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，【現行】の内容と合わせて，本申請に係る並びに記載整備を含む【変更】の内容を次ページより示す。

【現行】

<table>
<tr><td>化学名・別名</td><td>ウステキヌマブ（遺伝子組換え）</td></tr>
<tr><td>構造式</td><td>別紙</td></tr>
<tr><td>効能・効果</td><td>中等症から重症の活動期クローン病の導入療法（既存治療で効果不十分な場合に限る）
中等症から重症の潰瘍性大腸炎の寛解導入療法（既存治療で効果不十分な場合に限る）</td></tr>
<tr><td>用法・用量</td><td>通常，成人にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。
<table>
<tr><td>患者体重</td><td>投与量</td></tr>
<tr><td>55kg以下</td><td>260mg</td></tr>
<tr><td>55kgを超える85kg以下</td><td>390mg</td></tr>
<tr><td>85kgを超える</td><td>520mg</td></tr>
</table></td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>市販名：ステラーラ点滴静注 130mg（1 バイアル中 130mg 含有）
有効成分：ウステキヌマブ（遺伝子組換え）</td></tr>
<tr><td>毒性</td><td>単回投与毒性
<table>
<tr><td>動物種</td><td>投与経路</td><td>概略の致死量 1)
（mg/kg）</td></tr>
<tr><td>サル</td><td>静脈内投与</td><td>♂：>9</td></tr>
</table>
1)：単回静脈内投与による薬物動態試験の結果から求めた。
反復投与毒性
<table>
<tr><td>動物種</td><td>投与期間
投与経路</td><td>性別</td><td>投与量 1)
（mg/kg）</td><td>無毒性量
（mg/kg）</td><td>主な所見</td></tr>
<tr><td>サル</td><td>4週間
静脈内投与</td><td>♂♀</td><td>0, 9, 45</td><td>♂♀：45</td><td>特記すべき所見なし</td></tr>
</table>
1)：週 1 回投与</td></tr>
<tr><td>副作用</td><td>クローン病
副作用発現率（臨床検査値異常変動を含む）　188／941 例＝20.0%
［国際共同第III相試験（CNTO1275CRD3001 試験及び CNTO1275CRD3002 試験）］
<table>
<tr><td>副作用の種類</td><td>例数</td><td>臨床検査値異常の種類</td><td>例数</td></tr>
<tr><td>頭痛</td><td>29 例</td><td>体温上昇</td><td>2 例</td></tr>
<tr><td>悪心</td><td>14 例</td><td>肝機能検査異常</td><td>2 例</td></tr>
<tr><td>上気道感染</td><td>12 例</td><td>アラニンアミノトランスフェラーゼ増加</td><td>1 例</td></tr>
<tr><td>嘔吐</td><td>11 例</td><td>血中クレアチン増加</td><td>1 例</td></tr>
<tr><td>鼻咽頭炎</td><td>10 例</td><td>ヘモグロビン減少</td><td>1 例</td></tr>
<tr><td></td><td>等</td><td></td><td>等</td></tr>
</table>
潰瘍性大腸炎
副作用発現率（臨床検査値異常変動を含む）　81／641 例＝12.6%
［国際共同第III相試験（CNTO1275UCO3001 試験）］
<table>
<tr><td>副作用の種類</td><td>例数</td><td>臨床検査値異常の種類</td><td>例数</td></tr>
<tr><td>頭痛</td><td>10 例</td><td>リンパ球数減少</td><td>1 例</td></tr>
<tr><td>そう痒症</td><td>8 例</td><td>血中リン減少</td><td>1 例</td></tr>
<tr><td>疲労</td><td>7 例</td><td>好中球数減少</td><td>1 例</td></tr>
<tr><td>上気道感染</td><td>6 例</td><td>白血球数減少</td><td>1 例</td></tr>
<tr><td>リンパ球減少症</td><td>5 例</td><td></td><td></td></tr>
<tr><td></td><td>等</td><td></td><td></td></tr>
</table></td></tr>
</table>

会社	ヤンセンファーマ株式会社　製剤：製造

別紙

ウステキヌマブの重鎖（Heavy Chain）及び軽鎖（Light Chain）のアミノ酸配列

Heavy Chain

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY    60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS   120

STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG   180
                     146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP   240
                                222      228    231
                                LC       HC     HC          N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS   300
                          263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL   360

TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ   420
   369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                     449
```

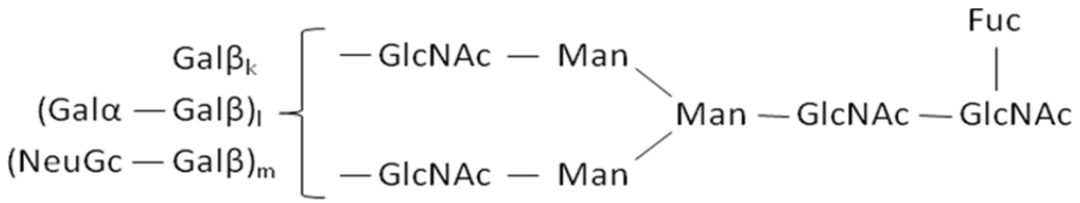
Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS    60
                          23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP   120

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT   180
                    134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                               214
                                    HC
```

下線部：相補性決定部；H 鎖 K449：部分プロセシング

糖鎖構造



k, l, m = 0, 1, 2;　k + l + m = 0, 1, 2

【変更】

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td>別紙（記載整備）</td></tr>
<tr><td>効能・効果</td><td></td></tr>
<tr><td>用法・用量</td><td>〈クローン病/ 潰瘍性大腸炎〉
成人
通常，成人にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。
<table>
<tr><td>患者体重</td><td>投与量</td></tr>
<tr><td>55kg以下</td><td>260mg</td></tr>
<tr><td>55kgを超える85kg以下</td><td>390mg</td></tr>
<tr><td>85kgを超える</td><td>520mg</td></tr>
</table>
〈クローン病〉
小児
通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，導入療法の初回に，以下に示す用量を単回点滴静注する。
<table>
<tr><td>患者体重</td><td>投与量</td></tr>
<tr><td>40kg未満</td><td>250mg/m^2（体表面積）</td></tr>
<tr><td>40kg以上55kg以下</td><td>260mg</td></tr>
<tr><td>55kgを超える85kg以下</td><td>390mg</td></tr>
<tr><td>85kgを超える</td><td>520mg</td></tr>
</table>
（下線部追加）</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td></td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>クローン病
副作用発現率（臨床検査値異常変動を含む）　188／941 例＝20.0%
［国際共同第III相試験（CNTO1275CRD3001 試験及び CNTO1275CRD3002 試験）］
<table>
<tr><td>副作用の種類</td><td>例数</td><td>臨床検査値異常の種類</td><td>例数</td></tr>
<tr><td>頭痛</td><td>29 例</td><td>体温上昇</td><td>2 例</td></tr>
<tr><td>悪心</td><td>14 例</td><td>肝機能検査異常</td><td>2 例</td></tr>
<tr><td>上気道感染</td><td>12 例</td><td>アラニンアミノトランスフェラーゼ増加</td><td>1 例</td></tr>
<tr><td>嘔吐</td><td>11 例</td><td>血中クレアチン増加</td><td>1 例</td></tr>
<tr><td>鼻咽頭炎</td><td>10 例</td><td>ヘモグロビン減少</td><td>1 例</td></tr>
<tr><td></td><td>等</td><td></td><td>等</td></tr>
</table>
潰瘍性大腸炎
副作用発現率（臨床検査値異常変動を含む）　81／641 例＝12.6%
［国際共同第III相試験（CNTO1275UCO3001 試験）］
<table>
<tr><td>副作用の種類</td><td>例数</td><td>臨床検査値異常の種類</td><td>例数</td></tr>
<tr><td>頭痛</td><td>10 例</td><td>リンパ球数減少</td><td>1 例</td></tr>
<tr><td>そう痒症</td><td>8 例</td><td>血中リン減少</td><td>1 例</td></tr>
<tr><td>疲労</td><td>7 例</td><td>好中球数減少</td><td>1 例</td></tr>
<tr><td>上気道感染</td><td>6 例</td><td>白血球数減少</td><td>1 例</td></tr>
<tr><td>リンパ球減少症</td><td>5 例</td><td></td><td></td></tr>
<tr><td></td><td>等</td><td></td><td></td></tr>
</table></td></tr>
</table>

	クローン病（小児） 副作用発現率（臨床検査値異常変動を含む）　8／101 例＝7.9% ［国際共同第III相試験（CNTO1275CRD3004 試験）］ 副作用の種類　例数　臨床検査値異常の種類　例数 頭痛　2 例　報告なし 嘔吐　2 例 等 （下線部追加）
会社	

別紙

ウステキヌマブの重鎖（H 鎖）及び軽鎖（L 鎖）のアミノ酸配列及びジスルフィド結合

H鎖

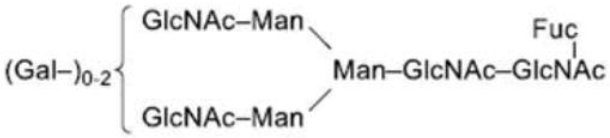
```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI       50
MSPVDSDIRY SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR      100
PGQGYFDFWG QGTLVTVSSS STKGPSVFPL APSSKSTSGG TAALGCLVKD      150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY      200
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK      250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS      300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV      350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL      400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK       449
```

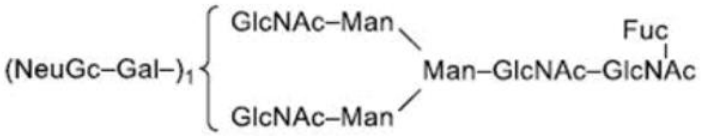
L鎖

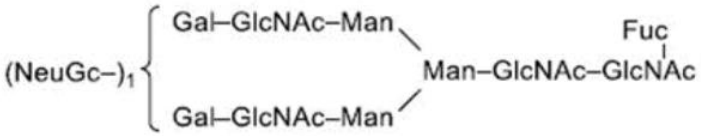
```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA       50
ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ      100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV      150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG      200
LSSPVTKSFN RGEC                                             214
```

H鎖E1：部分的ピログルタミン酸；H鎖N299：糖鎖結合；H鎖K449：部分的プロセシング
H鎖C222－L鎖C214，H鎖C228－H鎖C228，H鎖C231－H鎖C231：ジスルフィド結合

主な糖鎖の推定構造







$C_{6482}H_{10004}N_{1712}O_{2016}S_{46}$（タンパク質部分，4 本鎖）

H 鎖　$C_{2207}H_{3410}N_{582}O_{671}S_{17}$

L 鎖　$C_{1034}H_{1596}N_{274}O_{337}S_{6}$

1.10 毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について，【現行】の内容と合わせて，本申請に係る並びに記載整備を含む【変更】の内容を次ページより示す。

【現行】

化学名・別名	ウステキヌマブ（遺伝子組換え）
構造式	別紙
効能・効果	既存治療で効果不十分な下記疾患 尋常性乾癬，関節症性乾癬 中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る） 中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る）
用法・用量	尋常性乾癬及び関節症性乾癬 通常，成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し，以降 12 週間隔で投与する。 ただし，効果不十分な場合には 1 回 90mg を投与することができる。 クローン病/潰瘍性大腸炎 ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し，以降は 12 週間隔で 90mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。
劇薬等の指定	
市販名及び有効成分・分量	市販名：ステラーラ皮下注 45mg シリンジ（1 シリンジ中 45mg 含有） 有効成分：ウステキヌマブ（遺伝子組換え）
毒性	単回投与毒性 動物種：サル／投与経路：皮下／概略の致死量 1)（mg/kg）：♂♀：>45 1)：単回投与毒性試験を実施していないため，26 週間反復皮下投与毒性試験の初回投与時の結果から求めた。 反復投与毒性 動物種：サル／投与期間 投与経路：26週間 皮下／性別：♂♀／投与量 1)（mg/kg）：0, 22.5, 45／無毒性量（mg/kg）：♂♀：45／主な所見：特記すべき所見なし 1)：週2回投与
副作用	乾癬 副作用発現率（臨床検査値異常変動を含む）　154／172例＝89.5% ［国内第I相試験（JNS009-JPN-01試験）及び国内第II/III相試験（JNS009-JPN-02試験）］ 副作用の種類／例数：鼻咽頭炎 77例，アレルギー性鼻炎 14例，湿疹 10例，頭痛 9例，高血圧 9例，等 臨床検査値異常の種類／例数：肝機能検査異常 32例，血中クレアチンホスホキナーゼ増加 24例，血中トリグリセリド増加 23例，リンパ球数減少 17例，白血球数増加 12例，等 クローン病 副作用発現率（臨床検査値異常変動を含む）　98／314例＝31.2% ［国際共同第III相試験（CNTO1275CRD3003試験）］ 副作用の種類／例数：上気道感染 10例 臨床検査値異常の種類／例数：心拍数増加 2例

	注射部位紅斑 10例 頭痛 10例 発疹 8例 鼻咽頭炎 7例 悪心 7例 等 肝機能検査異常 2例 等 潰瘍性大腸炎 副作用発現率（臨床検査値異常変動を含む） 76／348例＝21.8% ［国際共同第III相試験（CNTO1275UCO3001試験）］ 副作用の種類 例数 上咽頭炎 11例 潰瘍性大腸炎 8例 上気道感染 7例 発疹 7例 頭痛 6例 等 臨床検査値異常の種類 例数 肝機能検査異常 5例 白血球数減少 2例 ブドウ球菌検査陽性 1例 リンパ球形態異常 1例 血中リン減少 1例 好中球数減少 1例 体重減少 1例 等
会社	ヤンセンファーマ株式会社　製剤：製造

別紙

ウステキヌマブの重鎖（HeavyChain）及び軽鎖（LightChain）のアミノ酸配列

Heavy Chain

```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI MSPVDSDIRY   60
                          22-96
SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR PGQGYFDFWG QGTLVTVSSS  120

STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG  180
                          146-202
LYSLSSVVTV PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP  240
                                    222 LC  228 HC  231 HC  N-Glycan
SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS  300
                          263-323
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL  360

TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ  420
   369-427
QGNVFSCSVM HEALHNHYTQ KSLSLSPGK                                    449
```

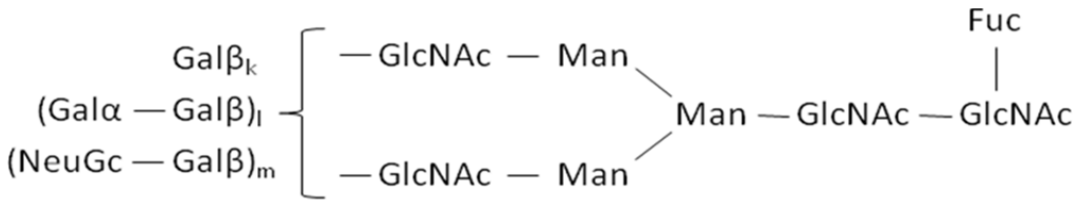
Light Chain

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA ASSLQSGVPS   60
                          23-88
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ GTKLEIKRTV AAPSVFIFPP  120

SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT  180
                    134-194
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC                              214
                                    HC
```

下線部：相補性決定部；H 鎖 K449：部分プロセシング

糖鎖構造



k, l, m = 0, 1, 2;　k + l + m = 0, 1, 2

【変更】

化学名・別名	
構造式	別紙（記載整備）
効能・効果	既存治療で効果不十分な下記疾患 尋常性乾癬，乾癬性関節炎 中等症から重症の活動期クローン病の維持療法（既存治療で効果不十分な場合に限る） 中等症から重症の潰瘍性大腸炎の維持療法（既存治療で効果不十分な場合に限る） （波線部記載整備）
用法・用量	尋常性乾癬及び乾癬性関節炎 通常，成人にはウステキヌマブ（遺伝子組換え）として 1 回 45mg を皮下投与する。初回投与及びその 4 週後に投与し，以降 12 週間隔で投与する。 ただし，効果不十分な場合には 1 回 90mg を投与することができる。 クローン病/潰瘍性大腸炎 成人 ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，成人にはウステキヌマブ（遺伝子組換え）として 90mg を皮下投与し，以降は 12 週間隔で 90mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。 クローン病 小児 ウステキヌマブ（遺伝子組換え）の点滴静注製剤を投与 8 週後に，通常，2 歳以上の小児にはウステキヌマブ（遺伝子組換え）として，体重 40kg 未満では 60mg/m^2（体表面積），体重 40kg 以上では 90mg を皮下投与する。以降は 12 週間隔で体重 40kg 未満では 60mg/m^2（体表面積），体重 40kg 以上では 90mg を皮下投与する。なお，効果が減弱した場合には，投与間隔を 8 週間に短縮できる。 （下線部変更・追加） （波線部記載整備）
劇薬等の指定	
市販名及び有効成分・分量	市販名： ステラーラ皮下注 45mg シリンジ（1 シリンジ中 45mg 含有） ステラーラ皮下注 45mg バイアル（1 バイアル中 45mg 含有） 有効成分：ウステキヌマブ（遺伝子組換え） （下線部追加）
毒性	
副作用	乾癬 副作用発現率（臨床検査値異常変動を含む）　154／172例＝89.5% ［国内第I相試験（JNS009-JPN-01試験）及び国内第II/III相試験（JNS009-JPN-02試験）］ 副作用の種類　例数 鼻咽頭炎　77例 アレルギー性鼻炎　14例 湿疹　10例 頭痛　9例 高血圧　9例 等 臨床検査値異常の種類　例数 肝機能検査異常　32例 血中クレアチンホスホキナーゼ増加　24例 血中トリグリセリド増加　23例 リンパ球数減少　17例 白血球数増加　12例 等 クローン病

	副作用発現率（臨床検査値異常変動を含む）　98／314例＝31.2% ［国際共同第III相試験（CNTO1275CRD3003試験）］ 副作用の種類　例数　臨床検査値異常の種類　例数 上気道感染　10例　心拍数増加　2例 注射部位紅斑　10例　肝機能検査異常　2例 頭痛　10例　等 発疹　8例 鼻咽頭炎　7例 悪心　7例 等 潰瘍性大腸炎 副作用発現率（臨床検査値異常変動を含む）　76／348例＝21.8% ［国際共同第III相試験（CNTO1275UCO3001試験）］ 副作用の種類　例数　臨床検査値異常の種類　例数 上咽頭炎　11例　肝機能検査異常　5例 潰瘍性大腸炎　8例　白血球数減少　2例 上気道感染　7例　ブドウ球菌検査陽性　1例 発疹　7例　リンパ球形態異常　1例 頭痛　6例　血中リン減少　1例 等　好中球数減少　1例 体重減少　1例 等 クローン病（小児） 副作用発現率（臨床検査値異常変動を含む）　3／97 例＝3.1% ［国際共同第III相試験（CNTO1275CRD3004 試験）］ 副作用の種類　例数　臨床検査値異常の種類　例数 上咽頭炎　1 例　報告なし 上気道感染　1 例 頭痛　1 例 発疹　1 例 （下線部追加）
会社	

別紙

ウステキヌマブの重鎖（H 鎖）及び軽鎖（L 鎖）のアミノ酸配列及びジスルフィド結合

H鎖

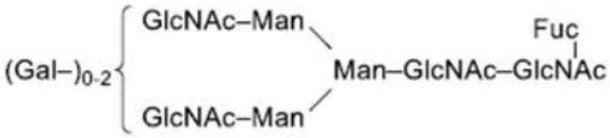
```
EVQLVQSGAE VKKPGESLKI SCKGSGYSFT TYWLGWVRQM PGKGLDWIGI        50
MSPVDSDIRY SPSFQGQVTM SVDKSITTAY LQWNSLKASD TAMYYCARRR       100
PGQGYFDFWG QGTLVTVSSS STKGPSVFPL APSSKSTSGG TAALGCLVKD       150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY       200
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK       250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS       300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV       350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL       400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK        449
```

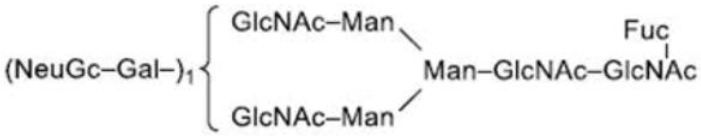
L鎖

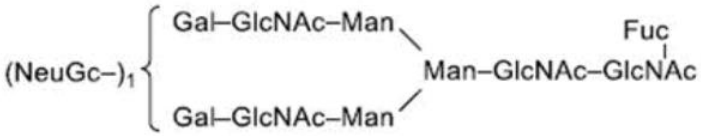
```
DIQMTQSPSS LSASVGDRVT ITCRASQGIS SWLAWYQQKP EKAPKSLIYA        50
ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNIYPYTFGQ       100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV       150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG       200
LSSPVTKSFN RGEC                                              214
```

H鎖E1：部分的ピログルタミン酸；H鎖N299：糖鎖結合；H鎖K449：部分的プロセシング
H鎖C222－L鎖C214，H鎖C228－H鎖C228，H鎖C231－H鎖C231：ジスルフィド結合

主な糖鎖の推定構造







$C_{6482}H_{10004}N_{1712}O_{2016}S_{46}$（タンパク質部分，4 本鎖）

H 鎖　$C_{2207}H_{3410}N_{582}O_{671}S_{17}$

L 鎖　$C_{1034}H_{1596}N_{274}O_{337}S_{6}$

添付資料番号	タイトル	掲載誌	評価資料 参考資料
3.2 データ又は報告書			
3.2.S 原薬			
	該当資料なし		
3.2.P 製剤			
3.2.P.1 製剤及び処方			
	Description and Composition of the Drug Product	社内資料	評価資料
3.2.P.2 製剤開発の経緯			
3.2.P.2.1 製剤成分			
	Drug Substance	社内資料	評価資料
	Excipients	社内資料	評価資料
3.2.P.2.2 製剤			
	Formulation Development	社内資料	評価資料
	Formulation Development [redacted]	社内資料	評価資料
	Overages	社内資料	評価資料
	Physiochemical and Biological Properties	社内資料	評価資料
3.2.P.2.3 製造工程の開発の経緯			
	Manufacturing Process Development [redacted]	社内資料	評価資料
	Manufacturing Process Development - FVP ([redacted]	社内資料	評価資料
	Manufacturing Process Development	社内資料	評価資料
	Manufacturing Process Development History of Test Methods and Specifications	社内資料	評価資料
3.2.P.2.4 容器及び施栓系			
	Container Closure System	社内資料	評価資料
3.2.P.2.5 微生物学的観点からみた特徴			
	Microbiological Attributes	社内資料	評価資料
3.2.P.2.6 溶解液や使用時の容器／用具との適合性			
	Compatibility	社内資料	評価資料
3.2.P.3 製造			
3.2.P.3.1 製造者			
	Manufacturer(s)	社内資料	評価資料
3.2.P.3.2 製造処方			
	Batch Formula	社内資料	評価資料
3.2.P.3.3 製造工程及びプロセス・コントロール			
	Description of Manufacturing Process and Process Controls [redacted]	社内資料	評価資料
	Description of Manufacturing Process and Process Controls FVP ([redacted]	社内資料	評価資料
3.2.P.3.4 重要工程及び重要中間体の管理			
	Controls of Critical Steps and Intermediates In-process Controls [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Justification of In-process Controls [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Critical Process Parameter Selection Process [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates In-process Controls FVP ([redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Justification of In-process Controls FVP ([redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Analytical Procedures - [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Analytical Procedures - [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Validation of Analytical Procedures - [redacted]	社内資料	評価資料
	Controls of Critical Steps and Intermediates Validation of Analytical Procedures - [redacted]	社内資料	評価資料
3.2.P.3.5 プロセス・バリデーション／プロセス評価			
	Process Validation and/or Evaluation Process Validation Overview [redacted]	社内資料	評価資料

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	Process Validation and/or Evaluation Validation of Process Steps [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation CNTO 1275 FVP Process Validation [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation Sterilization of [redacted], [redacted], [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation Comparability [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation Decontamination of the [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation [redacted] of [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation [redacted] [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation [redacted] [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation [redacted] [redacted]- [redacted]	社内資料	評価資料
	Process Validation and/or Evaluation [redacted] [redacted]	社内資料	評価資料
	Extractable and Leachable Risk Assessment of [redacted]Product Contact Materials	社内資料	評価資料
	[redacted]	社内資料	評価資料
	[redacted]	社内資料	評価資料
	[redacted]	社内資料	評価資料
	[redacted]	社内資料	評価資料
	[redacted]	社内資料	評価資料
	[redacted]	社内資料	評価資料
	Process Validation and/or Evaluation - Process Validation Overview-PFS, FVP ([redacted]/[redacted]	社内資料	評価資料
	Process Validation and/or Evaluation - Validation of Process Steps - PFS, FVP [redacted]([redacted]/[redacted]	社内資料	評価資料
	Process Validation and/or Evaluation - Comparability - FVP ([redacted]/[redacted]	社内資料	評価資料
	Process Validation and/or Evaluation - [redacted] FVP [redacted]/[redacted]	社内資料	評価資料
	Process Validation and/or Evaluation - [redacted] [redacted]Process Characterization - FVP ([redacted] [redacted]/[redacted]	社内資料	評価資料
3.2.P.4 添加剤の管理			
3.2.P.4.1 規格及び試験方法			
	Specifications	社内資料	評価資料
3.2.P.4.2 試験方法（分析方法）			
	Analytical Procedures	社内資料	評価資料
3.2.P.4.3 試験方法（分析方法）のバリデーション			
	Validation of Analytical Procedures	社内資料	評価資料
3.2.P.4.4 規格及び試験方法の妥当性			
	Justification of Specifications	社内資料	評価資料
3.2.P.4.5 ヒト又は動物起源の添加剤			
	Excipients of Human or Animal Origin	社内資料	評価資料
3.2.P.4.6 新規添加剤			
	Novel Excipients	社内資料	評価資料
3.2.P.5 製剤の管理			
3.2.P.5.1 規格及び試験方法			
	Specification(s)	社内資料	評価資料
3.2.P.5.2 試験方法（分析方法）			
	該当資料なし		
3.2.P.5.3 試験方法（分析方法）のバリデーション			

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	該当資料なし		
3.2.P.5.4 ロット分析			
	Batch Analyses Final Vialed Product (FVP) [redacted]	社内資料	評価資料
	Batch Analyses FVP, PFS and FVP (IV) [redacted]	社内資料	評価資料
	Batch Analyses PFS, FVP [redacted]	社内資料	評価資料
3.2.P.5.5 不純物の特性			
	該当資料なし		
3.2.P.5.6 規格及び試験方法の妥当性			
	Justification of Specification(s) cIEF	社内資料	評価資料
	Justification of Specification(s) Color of Solution	社内資料	評価資料
	Justification of Specification(s) cSDS	社内資料	評価資料
	Justification of Specification(s) Dot Blot	社内資料	評価資料
	Justification of Specification(s) DW-SE-HPLC	社内資料	評価資料
	Justification of Specification(s) Endotoxin	社内資料	評価資料
	Justification of Specification(s) Introduction	社内資料	評価資料
	Justification of Specification(s) [redacted]	社内資料	評価資料
	Justification of Specification(s) Particulate Matter ([redacted]	社内資料	評価資料
	Justification of Specification(s) Particulate Matter ([redacted]	社内資料	評価資料
	Justification of Specification(s) pH	社内資料	評価資料
	Justification of Specification(s) Protein Concentration by A280	社内資料	評価資料
	Justification of Specification(s) Sterility	社内資料	評価資料
	Justification of Specification(s) Turbidity	社内資料	評価資料
	Justification of Specification(s) Extractable Volume	社内資料	評価資料
	Justification of Specification(s) Bioactivity	社内資料	評価資料
3.2.P.6 標準品又は標準物質			
	該当資料なし		
3.2.P.7 容器及び施栓系			
	Container Closure System	社内資料	評価資料
3.2.P.8 安定性			
3.2.P.8.1 安定性のまとめ及び結論			
	Stability Summary and Conclusion - [redacted]	社内資料	評価資料
	Stability Summary and Conclusion - FVP [redacted]	社内資料	評価資料
	Stability Summary and Conclusion - FVP [redacted]	社内資料	評価資料
	Stability Summary and Conclusion	社内資料	評価資料
3.2.P.8.2 承認後の安定性試験計画の作成及び実施			
	Post-approval Stability Protocol and Stability Commitment - Stability Commitment - Post - approval - FVP ([redacted]	社内資料	評価資料
3.2.P.8.3 安定性データ			
	Stability data tables of Stelata FVP batches in [redacted] from [redacted] to [redacted]	社内資料	評価資料
	Stability data tables for Stelara FVP batch [redacted]	社内資料	評価資料
	Stability Data Tables for Stelara Final Vialed Product (FVP) Batch ([redacted]	社内資料	評価資料
3.2.A その他			
3.2.A.1 製造施設及び設備			
	Facilities and Equipment Manufacturing Flow- [redacted]	社内資料	評価資料
	Facilities and Equipment Facilities - [redacted]	社内資料	評価資料
	Facilities and Equipment Contamination Precautions [redacted]	社内資料	評価資料
	Facilities and Equipment Other Products - [redacted]	社内資料	評価資料
	Facilities and Equipment Equipment - [redacted]	社内資料	評価資料

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	[redacted]Cleaning Validation Report for the [redacted]of Stelara FVP IV and Filling [redacted]of Stelara FVP IV and Stelara PFS	社内資料	評価資料
	[redacted]Cleaning Validation Report for [redacted]with Stelara	社内資料	評価資料
	[redacted]Cleaning Validation Report for [redacted]L Vessels for Stelara	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Zone Concept Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Pharmaceutical Zones Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of liquid products in Vials Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid)	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes (liquid) Building [redacted]	社内資料	評価資料
	Flow of SCF syringes Building [redacted]	社内資料	評価資料
	Flow of SCF syrignes (liquid) Building [redacted]	社内資料	評価資料
	Material Flow Building [redacted]	社内資料	評価資料
	Flow of Material Building [redacted]	社内資料	評価資料
3.2.A.2 外来性感染性物質の安全性評価			
	該当資料なし		
3.2.A.3 添加剤			
	該当資料なし		
3.2.R 各極の要求資料			
	該当資料なし		
3.3 参考文献			
	該当資料なし		

添付資料番号	タイトル	掲載誌	評価資料 参考資料
4.2 試験報告書			
4.2.1 薬理試験			
4.2.1.1 効力を裏付ける試験			
	該当資料なし		
4.2.1.2 副次的薬理試験			
	該当資料なし		
4.2.1.3 安全性薬理試験			
	該当資料なし		
4.2.1.4 薬力学的薬物相互作用試験			
	該当資料なし		
4.2.2 薬物動態試験			
4.2.2.1 分析法及びバリデーション報告書			
	該当資料なし		
4.2.2.2 吸収			
	該当資料なし		
4.2.2.3 分布			
	該当資料なし		
4.2.2.4 代謝			
	該当資料なし		
4.2.2.5 排泄			
	該当資料なし		
4.2.2.6 薬物動態学的薬物相互作用（非臨床）			
	該当資料なし		
4.2.2.7 その他の薬物動態試験			
	該当資料なし		
4.2.3 毒性試験			
4.2.3.1 単回投与毒性試験			
	該当資料なし		
4.2.3.2 反復投与毒性試験			
	該当資料なし		
4.2.3.3 遺伝毒性試験			
4.2.3.3.1 *In Vitro*試験			
	該当資料なし		
4.2.3.3.2 *In Vivo*試験			
	該当資料なし		
4.2.3.4 がん原性試験			
4.2.3.4.1 長期がん原性試験			
	該当資料なし		
4.2.3.4.2 短期又は中期がん原性試験			
	該当資料なし		
4.2.3.4.3 その他の試験			
	該当資料なし		
4.2.3.5 生殖発生毒性試験			
4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験			
	該当資料なし		
4.2.3.5.2 胚・胎児発生に関する試験			
	該当資料なし		
4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験			
	該当資料なし		
4.2.3.5.4 新生児を用いた試験			
	該当資料なし		
4.2.3.6 局所刺激性試験			
	該当資料なし		
4.2.3.7 その他の毒性試験			
4.2.3.7.1 抗原性試験			

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	該当資料なし		
4.2.3.7.2 免疫毒性試験			
	該当資料なし		
4.2.3.7.3 毒性発現の機序に関する試験			
	該当資料なし		
4.2.3.7.4 依存性試験			
	該当資料なし		
4.2.3.7.5 代謝物の毒性試験			
	該当資料なし		
4.2.3.7.6 不純物の毒性試験			
	該当資料なし		
4.2.3.7.7 その他の試験			
	該当資料なし		
4.3 参考文献			
4.3.1	参考文献	参考文献を添付	参考資料

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.2 全臨床試験一覧表				
5.3 臨床試験報告書				
5.3.1 生物薬剤学試験報告書				
5.3.1.1 バイオアベイラビリティ（BA）試験報告書				
	該当資料なし			
5.3.1.2 比較BA試験及び生物学的同等性（BE）試験報告書				
	該当資料なし			
5.3.1.3 In Vitro－In Vivo の関連を検討した試験報告書				
	該当資料なし			
5.3.1.4 生物学的及び理化学的分析法検討報告書				
5.3.1.4.1-1	CP2008V-054_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054	参考資料	無
5.3.1.4.1-2	CP2008V-054-A2_Validation of an Electrochemiluminescent-Based Immunoassay for the Quantification of CNTO1275 in Human Serum: Incurred Sample Reproducibility Assessment	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A2	参考資料	無
5.3.1.4.1-3	CP2008V-054-A6_Addendum To: Validation of an Assay for the Quantification of CNTO1275 in Human Serum Using an Electrochemiluminescent Immunoassay - Stability of CNTO 1275 in Human Serum at Room Temperature for 8 Days and at -70°C for 5 Years	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A6	参考資料	無
5.3.1.4.1-4	CP2008V-054-A13_Partial Validation of the Meso Scale Discovery Electrochemiluminescent Immunoassay Method for the Quantification of CNTO 1275 in Human Serum: New Drug Stock Formulation, New Automated Liquid Handling Wizard Script Methods, and Selectivity Testing in Ankylosing Spondylitis, Systemic Lupus Erythematosus, and Ulcerative Colitis Disease Matrix	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A13	参考資料	無
5.3.1.4.1-5	CP2008V-054-A14_Partial Validation of the Meso Scale Discovery Electrochemiluminescent Immunoassay Method for the Quantification of CNTO 1275 in Human Serum: Selectivity Testing in Ulcerative Colitis Disease Matrix, and Diluted Sample Stability	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A14	参考資料	無
5.3.1.4.1-6	CP2008V-054-A15_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform - Incurred Sample Reproducibility and Parallelism Assessment for Modified Method in Systemic Lupus Erythematosus	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A15	参考資料	無
5.3.1.4.1-7	CP2008V-054-A16_Partial Validation and Cross Validation of the Method for the Quantification of CNTO 1275 in Human Serum Following Its Transfer from [redacted] to the [redacted], and Additional Stability Testing	ヤンセンファーマ 社内資料 報告書番号： CP2008V-054-A16	参考資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.1.4.1-8	CP2008V-054-A17_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform - Incurred Sample Reproducibility and Parallelism Assessment for Ulcerative Colitis Disease Population	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A17	参考資料	無
5.3.1.4.1-9	CP2008V-054-A18_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform - Incurred Sample Reproducibility and Parallelism Assessment for Crohn's Disease Population	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A18	参考資料	無
5.3.1.4.1-10	CP2008V-054-A19_Partial Validation of the Meso Scale Discovery Electrochemiluminescent Immunoassay Method for the Quantification of CNTO 1275 In Human Serum: Supplemental Stability Testing	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A19	参考資料	無
5.3.1.4.1-11	CP2008V-054-A20_Partial Validation of the Meso Scale Discovery Electrochemiluminescent Immunoassay Method for the Quantification of CNTO 1275 in Human Serum: Selectivity Testing in Dermatomyositis Disease Matrix	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A20	参考資料	無
5.3.1.4.1-12	CP2008V-054-A21_Partial Validation of the Meso Scale Discovery Electrochemiluminescent Immunoassay Method for the Quantification of CNTO 1275(Stelara®) in Human Serum: Interference Testing with Remicade® (Infliximab), Enbrel® (Etanercept), Humira® (Adalimumab), Simponi® (Golimumab), Entyvio® (Vedolizumab) and Tremfya® (Guselkumab)	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A21	参考資料	無
5.3.1.4.1-13	CP2008V-054-A22_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform - Incurred Sample Reproducibility and Parallelism in Polymyositis and Dermatomyositis Disease Matrix at [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A22	参考資料	無
5.3.1.4.1-14	CP2008V-054-A23_Validation of an Assay for the Quantification of CNTO 1275 in Human Serum Using the Meso Scale Discovery Platform -Incurred Sample Reproducibility and Parallelism in Pediatric Populations at [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A23	参考資料	無
5.3.1.4.1-15	CP2008V-054-A24_Validation of an Electrochemiluminescence-Based Immunoassay for the Quantification of CNTO1275 in Human Serum on the Meso Scale Discovery (MSD®) Platform: Incurred Sample Reanalysis (ISR) and Sample Parallelism (PAR) in Pediatric Participants with Moderately to Severely Active Crohn's Disease. Assessment at [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A24	参考資料	無
5.3.1.4.1-16	CP2008V-054-A25_Validation of an Electrochemiluminescence-based Immunoassay for the Quantification of CNTO1275 in Human Serum on the MSD ® Platform: Incurred Sample Reanalysis and Sample Parallelism in Pediatric Participants With Moderately to Severely Active Crohn's Disease at [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2008V-054-A25	参考資料	無
5.3.1.4.2-1	CP2011V-035_Validation of an ECLIA Method to Detect Antibodies to Ustekinumab (CNTO 1275) in Human Serum Samples	ヤンセンファーマ社内資料 報告書番号： CP2011V-035	参考資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.1.4.2-2	CP2011V-035-A10_Amendment to Validation of an ECLIA Method to Detect Antibodies to Ustekinumab (CNTO 1275) in Human Serum Samples - Screening Cut Point Update	ヤンセンファーマ社内資料 報告書番号： CP2011V-035-A10	参考資料	無
5.3.1.4.2-3	CP2011V-035-A11_Partial and Cross-validation of an Electrochemiluminescent Assay to Detect Antibodies to Stelara® (Ustekinumab) in Human Serum Samples to Support Method Transfer from [redacted] to [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2011V-035-A11	参考資料	無
5.3.1.4.2-4	CP2011V-035-A12_Amendment to Validation of an ECLIA Method to Detect Antibodies to Ustekinumab (CNTO 1275) in Human Serum Samples: Long Term Stability Update	ヤンセンファーマ社内資料 報告書番号： CP2011V-035-A12	参考資料	無
5.3.1.4.2-5	CP2011V-035-A13_Partial Validation of a Method to Detect Antibodies to Stelara® (ustekinumab) in Serum Samples from Humans: Updates to meet 2019 FDA Guidance Requirements	ヤンセンファーマ社内資料 報告書番号： CP2011V-035-A13	参考資料	無
5.3.1.4.2-6	CP2011V-035-A14_Partial Validation of a Method to Detect Antibodies to Stelara® (ustekinumab) in Serum Samples from Humans: Assessment of Interference due to infliximab (Remicade®), Etanercept (Enbrel®), Adalimumab (Humira®), Golimumab (Simponi®), Vedolizumab (Entyvio®), And Guselkumab (Tremfya®)	ヤンセンファーマ社内資料 報告書番号： CP2011V-035-A14	参考資料	無
5.3.1.4.3-1	CP2010V-050_Validation of an Electrochemiluminescence-based Immunoassay to Detect Neutralizing Antibodies to Ustekinumab (CNTO 1275) in Human Serum	ヤンセンファーマ社内資料 報告書番号： CP2010V-050	参考資料	無
5.3.1.4.3-2	CP2010V-050-A2_Partial Validation of an Electrochemiluminescence-based Competitive Ligand Binding Assay Transferred from [redacted] to [redacted] for the Detection of Neutralizing Antibodies to Ustekinumab (CNTO 1275) in Human Serum	ヤンセンファーマ社内資料 報告書番号： CP2010V-050-A2	参考資料	無
5.3.1.4.3-3	CP2010V-050-A4_Partial Validation of the Ustekinumab (Stelara®) Neutralizing Antibody Assay (With Enhanced Drug Tolerance) for Combination Therapy of Ustekinumab (Stelara®) With Infliximab (Remicade®), Etanercept (Enbrel®), Adalimumab (Humira®), Golimumab (Simponi®), and Vedolizumab (Entyvio®)	ヤンセンファーマ社内資料 報告書番号： CP2010V-050-A4	参考資料	無
5.3.1.4.3-4	CP2010V-050-A5_Validation of an Electrochemiluminescence-based Immunoassay to Detect Neutralizing Antibodies to Ustekinumab (CNTO1275) in Human Serum: Revision of Acceptance Criteria for CNTO1275 NAb Assay Controls	ヤンセンファーマ社内資料 報告書番号： CP2010V-050-A5	参考資料	無
5.3.1.4.3-5	CP2010V-050-A6_Partial Validation of the Ustekinumab (Stelara®, CNTO1275) Neutralizing Antibody Assay With Enhanced Drug Tolerance to Assess the Cut Point in Human Serum Samples from Juvenile Psoriatic Arthritis (JPSA) and Pediatric Psoriasis (PPSO) Subjects	ヤンセンファーマ社内資料 報告書番号： CP2010V-050-A6	参考資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.1.4.3-6	CP2010V-050-A7_Cross-validation of an Electrochemiluminescence-based Immunoassay to Detect Neutralizing Antibodies to Ustekinumab (CNTO1275) in Human Serum Samples to Support Method Transfer from [redacted] to [redacted]	ヤンセンファーマ社内資料 報告書番号： CP2010V-050-A7	参考資料	無
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書				
5.3.2.1 血漿蛋白結合試験報告書				
	該当資料なし			
5.3.2.2 肝代謝及び薬物相互作用試験報告書				
	該当資料なし			
5.3.2.3 他のヒト生体試料を用いた試験報告書				
	該当資料なし			
5.3.3 臨床薬物動態（PK）試験報告書				
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書				
	該当資料なし			
5.3.3.2 患者におけるPK及び初期忍容性試験報告書				
5.3.3.2.1-1	A Randomized Double-blind Pharmacokinetic Study of Ustekinumab in Pediatric Subjects with Moderately to Severely Active Crohn's Disease (Week 16)	ヤンセンファーマ社内資料 試験番号： CNTO1275CRD1001	評価資料	有
5.3.3.2.1-2	A Randomized Double-blind Pharmacokinetic Study of Ustekinumab in Pediatric Subjects with Moderately to Severely Active Crohn's Disease (Long-term Extension)	ヤンセンファーマ社内資料 試験番号： CNTO1275CRD1001	評価資料	有
5.3.3.3 内因性要因を検討したPK試験報告書				
	該当資料なし			
5.3.3.4 外因性要因を検討したPK試験報告書				
	該当資料なし			
5.3.3.5 ポピュレーションPK試験報告書				
5.3.3.5.1	Population Pharmacokinetics & Exposure-Response Analysis Report for Ustekinumab in the Treatment of Pediatric Patients (2 to <18 years of Age) With Moderately to Severely Active Crohn's Disease	ヤンセンファーマ社内資料	参考資料	有
5.3.3.5.2	Population Pharmacokinetics & Exposure-Response Analysis Report for Ustekinumab in Pediatric Participants (≥40 kg) with Moderately to Severely Active Crohn's Disease (Induction Week 8 and Maintenance Week 44 Submission)	ヤンセンファーマ社内資料	参考資料	無
5.3.4 臨床薬力学（PD）試験報告書				
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書				
	該当資料なし			

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子データ有無
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書				
	該当資料なし			
5.3.5 有効性及び安全性試験報告書				
5.3.5.1 申請する適応症に関する比較対照試験報告書				
5.3.5.1.1	A Phase 3 Study of the Efficacy, Safety, and Pharmacokinetics of Ustekinumab as Open-label Intravenous Induction Treatment Followed by Randomized Double-blind Subcutaneous Ustekinumab Maintenance in Pediatric Participants 2 to <18 Years of Age With Moderately to Severely Active Crohn's Disease	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	有
5.3.5.1.2	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease Who Have Failed or Are Intolerant to TNF Antagonist Therapy	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.5.1.3	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.5.1.4-1	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease (44 Week)	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.5.1.4-2	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease (96 Week)	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.5.1.4-3	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease (272 Week)	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.5.2 非対照試験報告書				
	該当資料なし			
5.3.5.3 複数の試験成績を併せて解析した報告書				
5.3.5.3.1	Integrated Summary of CP	ヤンセンファーマ 社内資料	評価資料	無
5.3.5.3.2	Integrated Summary of Efficacy	ヤンセンファーマ 社内資料	評価資料	有
5.3.5.3.3	Integrated Summary of Safety	ヤンセンファーマ 社内資料	評価資料	有
5.3.5.4 その他の試験報告書				
5.3.5.4.1	CNTO1275CRD3004 (Japanese population)	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	有

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.3.5.4.2	Safety Report - CNTO1275ISD3001	ヤンセンファーマ 社内資料 試験番号： CNTO1275ISD3001	参考資料	無
5.3.6 市販後の使用経験に関する報告書				
5.3.6.1	Ustekinumab_PBRER	ヤンセンファーマ 社内資料	参考資料	無
5.3.7 患者データ一覧表及び症例記録				
5.3.7.1 用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表				
5.3.7.1.1	症例一覧表（試験番号：CNTO1275CRD3004）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	無
5.3.7.1.2	症例一覧表（試験番号：CNTO1275CRD3001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.7.1.3	症例一覧表（試験番号：CNTO1275CRD3002）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.7.1.4	症例一覧表（試験番号：CNTO1275CRD3003）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.7.2 実施された全ての臨床試験において副作用が観察された症例の一覧表				
5.3.7.2.1	副作用一覧表（試験番号：CNTO1275CRD1001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD1001	評価資料	無
5.3.7.2.2	副作用一覧表（試験番号：CNTO1275CRD3004）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	無
5.3.7.2.3	副作用一覧表（試験番号：CNTO1275CRD3001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.7.2.4	副作用一覧表（試験番号：CNTO1275CRD3002）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.7.2.5	副作用一覧表（試験番号：CNTO1275CRD3003）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.7.3 実施された全ての臨床試験において重篤な有害事象が観察された症例の一覧表				
5.3.7.3.1	重篤な有害事象一覧表（試験番号：CNTO1275CRD1001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD1001	評価資料	無
5.3.7.3.2	重篤な有害事象一覧表（試験番号：CNTO1275CRD3004）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	無
5.3.7.3.3	重篤な有害事象一覧表（試験番号：CNTO1275CRD3001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.7.3.4	重篤な有害事象一覧表（試験番号：CNTO1275CRD3002）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.7.3.5	重篤な有害事象一覧表（試験番号：CNTO1275CRD3003）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.3.7.4 実施された全ての臨床試験において臨床検査値異常変動が観察された症例の一覧表				
5.3.7.4.1	臨床検査値異常変動一覧表（試験番号：CNTO1275CRD1001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD1001	評価資料	無
5.3.7.4.2	臨床検査値異常変動一覧表（試験番号：CNTO1275CRD3004）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3004	評価資料	無
5.3.7.4.3	臨床検査値異常変動一覧表（試験番号：CNTO1275CRD3001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.7.4.4	臨床検査値異常変動一覧表（試験番号：CNTO1275CRD3002）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.7.4.5	臨床検査値異常変動一覧表（試験番号：CNTO1275CRD3003）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.3.7.5 実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図				
5.3.7.5.1	臨床検査値の変動図（試験番号：CNTO1275CRD3001）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3001	参考資料	無
5.3.7.5.2	臨床検査値の変動図（試験番号：CNTO1275CRD3002）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3002	参考資料	無
5.3.7.5.3	臨床検査値の変動図（試験番号：CNTO1275CRD3003）	ヤンセンファーマ 社内資料 試験番号： CNTO1275CRD3003	参考資料	無
5.4 参考文献				
5.4.1	参考文献	参考文献を添付	参考資料	無