イラリス皮下注射液 150mg に関する資料

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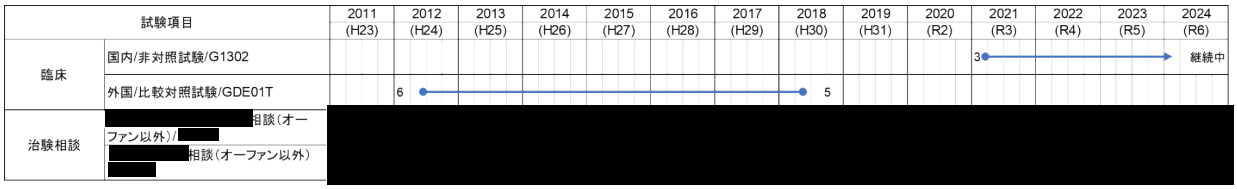
1 起原又は発見の経緯

起原又は発見の経緯については「2.5 臨床に関する概括評価」を参照。

2 開発の経緯

開発の経緯図を Figure 2-1 に示す。当該申請パッケージは臨床試験のみで構成され，品質に関する試験や非臨床試験はない。

Figure 2-1 開発の経緯図



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表 一 覧

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1 外国における使用状況等

カナキヌマブ（商品名：イラリス）は，クリオピリン関連周期性症候群（CAPS）の適応で 2009 年 6 月に米国で初めて承認され，2024 年 2 月現在，米国，EU，英国，カナダ，オーストラリアを含む世界 70 ヵ国以上で承認されている。今回適応追加を行う成人発症スチル病について，主要国における承認状況を，Table 1-1 に示す。

Table 1-1 主要国における承認状況

国名	承認年月日	効能・効果	用法・用量
米国	2020 年 6 月 16 日	**スチル病［成人発症スチル病（AOSD），及び全身型若年性特発性関節炎（SJIA）］** イラリスは，成人発症スチル病（AOSD）及び全身型若年性特発性関節炎（SJIA）を含む 2 歳以上の活動性スチル病の治療を適応症とする治療薬である。	**スチル病［成人発症スチル病（AOSD），及び全身型若年性特発性関節炎（SJIA）を含む］** 体重 7.5 kg 以上のスチル病（AOSD 及び SJIA）患者へのイラリスの推奨用量は 4 mg/kg であり（最高 300 mg），4 週ごとに皮下投与する。
EU	2016 年 8 月 1 日	スチル病 イラリスは，成人発症スチル病（AOSD）及び 2 歳以上で前治療の非ステロイド系抗炎症薬及び全身性コルチコステロイドにより十分な効果がみられなかった患者における活動性全身型若年性特発性関節炎（SJIA）を含む活性型スチル病を適応症とする治療薬である。イラリスは，単剤療法又はメトトレキサートとの併用療法として投与可能である。	スチル病（SJIA 及び AOSD） 体重 7.5 kg 以上のスチル病患者へのカナキヌマブの推奨用量は 4 mg/kg（最高 300 mg）であり，4 週ごとに皮下投与する。医師は，臨床的改善がみられない患者については，カナキヌマブの投与継続を再検討すること。

2 外国の添付文書等の概要

ノバルティスファーマ社の企業中核データシート（CDS，[redacted] 年 [redacted] 月 [redacted] 日改訂），米国の添付文書（2023 年 8 月 25 日改訂），及び欧州の共通の添付文書（2023 年 8 月 25 日改訂）を添付する。

NOVARTIS

[redacted]

ILARIS® (canakinumab)
150 mg Powder for solution for injection
150 mg/1 mL Solution for injection

Core Data Sheet (CDS)

[redacted]

2頁から42頁まで未公表のため削除

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ILARIS® (canakinumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

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

Indications and Usage, Gout Flares (1.3)	8/2023
Dosage and Administration, Gout Flares (2.5)	8/2023

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

ILARIS is an interleukin-1β blocker indicated for the treatment of:

- **Periodic Fever Syndromes** (1.1):
  - Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older, including:
    - Familial Cold Auto-inflammatory Syndrome (FCAS)
    - Muckle-Wells Syndrome (MWS)
  - Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients
  - Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients
  - Familial Mediterranean Fever (FMF) in adult and pediatric patients
- **Active Still's Disease,** including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older (1.2)
- **Gout flares** in adults in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (1.3)

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

- **CAPS:** Recommended weight-based dosage is:
  - For patients > 40 kg: 150 mg subcutaneously, every 8 weeks
  - For patients ≥ 15 kg and < 40 kg: 2 mg/kg subcutaneously, every 8 weeks. For pediatric patients 15 kg to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. (2.2)
- **TRAPS, HIDS/MKD, and FMF:** Recommended weight-based dosage is:
  - For patients > 40 kg: Starting dosage is 150 mg subcutaneously every 4 weeks. The dosage can be increased to 300 mg every 4 weeks if the clinical response is not adequate. (2.3)
  - For patients ≤ 40 kg: Starting dosage is 2 mg/kg subcutaneously every 4 weeks. The dosage can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate. (2.3)
- **Still's disease (AOSD and SJIA):** Recommended weight-based dosage for patients ≥ 7.5 kg is 4 mg/kg (maximum dose of 300 mg), subcutaneously, every 4 weeks. (2.4)
- **Gout Flares:** Recommended dosage is 150 mg subcutaneously. In patients who require re-treatment, there should be an interval of at least 12 weeks before a new dose of ILARIS may be administered. (2.5)

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

- Injection: 150 mg/mL solution in single-dose vials. (3)

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

Confirmed hypersensitivity to canakinumab or to any of the excipients. (4)

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

- Serious infections: ILARIS has been associated with an increased incidence of serious infections. Exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Discontinue ILARIS if a patient develops a serious infection. Avoid administering ILARIS to patients during an active infection requiring medical intervention. (5.1)
- Immunizations: Avoid administration of live vaccines concurrently with ILARIS. Update all recommended vaccinations prior to initiation of therapy with ILARIS. (5.4)

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

- **CAPS:** The most common adverse reactions (>10%) are nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo. (6)
- **TRAPS, HIDS/MKD, and FMF:** The most common adverse reactions (≥10%) are injection-site reactions and nasopharyngitis. (6)
- **Still's Disease:** The most common adverse drug reactions (>10%) are infections (nasopharyngitis and upper respiratory tract infections), abdominal pain, and injection-site reactions. (6)
- **Gout Flares:** The most common adverse reactions (>2%) reported by are nasopharyngitis, upper respiratory tract infections, urinary tract infections, hypertriglyceridemia, and back pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Periodic Fever Syndromes

ILARIS® (canakinumab) is an interleukin-1β (IL-1β) blocker indicated for the treatment of the following autoinflammatory Periodic Fever Syndromes:

Cryopyrin-Associated Periodic Syndromes (CAPS)

ILARIS is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and pediatric patients 4 years of age and older, including:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)

Tumor Necrosis Factor Receptor (TNF) Associated Periodic Syndrome (TRAPS)

ILARIS is indicated for the treatment of Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients.

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

ILARIS is indicated for the treatment of Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients.

Familial Mediterranean Fever (FMF)

ILARIS is indicated for the treatment of Familial Mediterranean Fever (FMF) in adult and pediatric patients.

1.2 Still's Disease (Adult-Onset Still's Disease [AOSD] and Systemic Juvenile Idiopathic Arthritis [SJIA])

ILARIS is indicated for the treatment of active Still's Disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older.

1.3 Gout Flares

ILARIS is indicated for the symptomatic treatment of adult patients with gout flares in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

ILARIS IS FOR SUBCUTANEOUS USE ONLY.

2.2 Recommended Dosage for Cryopyrin-Associated Periodic Syndromes (CAPS)

The recommended weight-based dosage of ILARIS is:

- For patients with CAPS > 40 kg: 150 mg subcutaneously, every 8 weeks
- For patients with CAPS ≥ 15 kg and ≤ 40 kg: 2 mg/kg subcutaneously, every 8 weeks.
- For pediatric patients with CAPS 15 kg to 40 kg with an inadequate response, the dosage can be increased to 3 mg/kg subcutaneously, every 8 weeks.

2.3 Recommended Dosage for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF)

The recommended weight-based dosage of ILARIS for patients with TRAPS, HIDS/MKD, and FMF is:

- For patients > 40 kg: 150 mg subcutaneously, every 4 weeks. The dosage can be increased to 300 mg every 4 weeks if the clinical response is not adequate.
- For patients ≤ 40 kg: 2 mg/kg administered subcutaneously, every 4 weeks. The dosage can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate.

2.4 Recommended Dosage for Still's Disease, Including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)

The recommended weight-based dosage of ILARIS for patients with Still's Disease (AOSD and SJIA) weighing ≥ 7.5 kg is 4 mg/kg (maximum dose of 300 mg) administered subcutaneously every 4 weeks.

2.5 Recommended Dosage for Gout Flares

The recommended dose of ILARIS for adult patients with a gout flare is 150 mg administered subcutaneously. In patients who require re-treatment, there should be an interval of at least 12 weeks before a new dose of ILARIS may be administered.

2.6 Administration Instructions for ILARIS Injection

STEP 1: ILARIS injection has a concentration of 150 mg/mL. Do not shake. The solution should be essentially free from particulates, clear to opalescent, colorless to slightly brownish-yellow tint. If the solution has a distinctly brown discoloration, is highly opalescent or contains visible particles, do not use.

STEP 2: Using a sterile 1-mL syringe and 18-gauge x 2" needle, carefully withdraw the required volume depending on the dose to be administered and subcutaneously inject using a 27-gauge x 0.5" needle.

Avoid injection into scar tissue as this may result in insufficient exposure to ILARIS.

Discard unused product or waste material in accordance with the local requirements.

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL, clear to slightly opalescent, colorless to a slightly brownish yellow tint solution, in single-dose vials.

4 CONTRAINDICATIONS

Confirmed hypersensitivity to canakinumab or to any of the excipients *[see Warnings and Precautions (5.3)* and *Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

ILARIS has been associated with an increased risk of serious infections. Exercise caution when administering ILARIS to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Avoid administering ILARIS to patients during an active infection requiring medical intervention. Discontinue ILARIS if a patient develops a serious infection.

Infections, predominantly of the upper respiratory tract, in some instances serious, have been reported with ILARIS. Generally, the observed infections responded to standard therapy. Isolated cases of unusual or opportunistic infections (e.g., aspergillosis, atypical mycobacterial infections, cytomegalovirus, herpes zoster) were reported during ILARIS treatment. A causal relationship of ILARIS to these events cannot be excluded. In clinical trials, ILARIS has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Coadministration of ILARIS with TNF inhibitors is not recommended because this may increase the risk of serious infections *[see Drug Interactions (7.1)]*.

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of new tuberculosis and reactivation of latent tuberculosis (TB). It is possible that use of IL-1 inhibitors, such as ILARIS, increases the risk of reactivation of tuberculosis or of opportunistic infections.

Prior to initiating immunomodulatory therapies, including ILARIS, evaluate patients for active and latent tuberculosis infection. Appropriate screening tests should be performed in all patients. ILARIS has not been studied in patients with a positive tuberculosis screen, and the safety of ILARIS in individuals with latent tuberculosis infection is unknown. Treat patients testing positive in tuberculosis screening according to standard medical practice prior to therapy with ILARIS. Instruct patients to seek medical advice if signs, symptoms, or high-risk exposure suggestive of tuberculosis (e.g., persistent cough, weight loss, subfebrile temperature) appear during or after ILARIS therapy.

Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ILARIS.

5.2 Immunosuppression

The impact of treatment with anti-interleukin-1 (IL-1) therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including ILARIS, may result in an increase in the risk of malignancies.

5.3 Hypersensitivity

Hypersensitivity reactions have been reported with ILARIS therapy. During clinical trials, no anaphylactic reactions attributable to treatment with canakinumab have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS. If a severe hypersensitivity reaction occurs, administration of ILARIS should be discontinued and appropriate therapy initiated *[see Contraindications (4)* and *Adverse Reactions (6.1)]*.

5.4 Immunizations

Avoid administration of live vaccines concurrently with ILARIS *[see Drug Interactions (7.2)]*. Since no data are available on either the efficacy or on the risks of secondary transmission of infection by live vaccines in patients receiving ILARIS, avoid administering live vaccines concurrently with ILARIS. In addition, because ILARIS may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ILARIS. Limited data are available on the response to vaccinations with inactivated (killed) antigens in patients receiving ILARIS *[see Drug Interactions (7.2)]*.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ILARIS, adult and pediatric patients receive all recommended vaccinations, as appropriate and if feasible, including pneumococcal vaccine and inactivated influenza vaccine. See current recommended immunization schedules at the website of the Centers for Disease Control, http://www.cdc.gov/vaccines/schedules/index.html.

5.5 Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease, and should be aggressively treated. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Eleven cases of MAS were observed in 201 SJIA patients treated with canakinumab in clinical trials. Based on the clinical trial experience, ILARIS does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Immunosuppression *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Warnings and Precautions (5.3)]*
- Macrophage Activation Syndrome *[see Warnings and Precautions (5.5)]*

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.

Adverse Reactions from Clinical Trials for Treatment of Periodic Fever Syndromes: CAPS, TRAPS, HIDS/MKD, and FMF

Treatment of CAPS

The data described herein reflect exposure to ILARIS in 104 adult and pediatric CAPS patients, including 20 FCAS, 72 MWS, 10 MWS/NOMID (Neonatal Onset Multisystem Inflammatory Disorder) overlap, 1 non-FCAS non-MWS, and 1 misdiagnosed in placebo-controlled (35 patients) and uncontrolled trials. Sixty-two patients were exposed to ILARIS for at least 6 months, 56 for at least 1 year, and 4 for at least 3 years. A total of 9 serious adverse reactions were reported for CAPS patients. Among these were vertigo (2 patients), infections (3 patients), including intra-abdominal abscess

following appendectomy (1 patient). The most commonly reported adverse reactions associated with ILARIS treatment in greater than 10% of the CAPS patients were nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, and vertigo. One patient discontinued treatment due to potential infection.

CAPS Study 1 investigated the safety of ILARIS in an 8-week, open-label period (Part 1), followed by a 24-week, randomized withdrawal period (Part 2), followed by a 16-week, open-label period (Part 3). All patients were treated with ILARIS 150 mg subcutaneously or 2 mg/kg if body weight was greater than or equal to 15 kg and less than or equal to 40 kg (see Table 1).

Since all CAPS patients received ILARIS in Part 1, there are no controlled data on adverse events (AEs). Data in Table 1 are for all AEs for all CAPS patients receiving canakinumab. In CAPS Study 1, no pattern was observed for any type or frequency of adverse events throughout the 3 study periods.

Table 1: Adverse Reactions in ≥10% of Patients in Parts 1 to 3 of the Phase 3 Trial for Patients with CAPS

Adverse reactions	**ILARIS N = 35 n (%)**
n (%) of patients with adverse reactions	35 (100)
Nasopharyngitis	12 (34)
Diarrhea	7 (20)
Influenza	6 (17)
Rhinitis	6 (17)
Nausea	5 (14)
Headache	5 (14)
Bronchitis	4 (11)
Gastroenteritis	4 (11)
Pharyngitis	4 (11)
Weight increased	4 (11)
Musculoskeletal pain	4 (11)
Vertigo	4 (11)

Vertigo

Vertigo has been reported in 9% to 14% of patients in CAPS studies, exclusively in MWS patients, and reported as a serious adverse event in 2 cases. All events resolved with continued treatment with ILARIS.

Injection-Site Reactions
In CAPS Study 1, subcutaneous injection-site reactions were observed in 9% of patients in Part 1 with mild tolerability reactions; in Part 2, one patient each (7%) had a mild or a moderate tolerability reaction and, in Part 3, one patient had a mild local tolerability reaction. No severe injection-site reactions were reported, and none led to discontinuation of treatment.

Treatment of TRAPS, HIDS/MKD, and FMF

A Phase 3 trial (TRAPS, HIDS/MKD, and FMF Study 1) investigated the safety of ILARIS in 3 cohorts (TRAPS, HIDS/MKD, and FMF) as follows: a 12-week screening period (Part 1), followed by a 16-week, randomized, double-blind, placebo-controlled parallel-arm treatment period (Part 2), followed by a 24-week randomized withdrawal period (Part 3), followed by a 72-week, open-label treatment period (Part 4). All patients randomized to treatment with ILARIS in Part 2 received 150 mg subcutaneously every 4 weeks if body weight was greater than 40 kg (or 2 mg/kg every 4 weeks if body weight was less than or equal to 40 kg).

In Part 2 of the TRAPS, HIDS/MKD, and FMF Study 1, initially 90 patients were randomized to ILARIS treatment, and 91 patients were randomized to placebo. Of patients randomized to ILARIS, 55.6% remained on the initial dose through Week 16 with 6.7% receiving an additional ILARIS dose between Day 7 and Day 15. Of the patients randomized to placebo, 9.9% remained on placebo through Week 16 with 28.6% switching to active treatment with ILARIS by Day 15.

Overall, there were 43 TRAPS, 68 HIDS/MKD, and 58 FMF patients in the safety set with a cumulative canakinumab exposure of 47.61 patient-years. The cumulative exposure in the placebo group was 8.03 patient-years.

In Part 2 of the TRAPS, HIDS/MKD, and FMF Study 1, a total of 22 TRAPS patients aged 3 to 76 years of age, 37 HIDS/MKD patients aged 2 to 43 years of age, and 31 FMF patients aged 2 to 60 years of age were initially randomized to treatment with ILARIS 150 mg every four weeks in the placebo-controlled period of the clinical trial. In addition, 4 non-randomized patients (2 FMF patients of age 20 and 29 years with non-exon 10 mutations and 2 HIDS/MKD patients both of 1 year of age) received open-label treatment in Part 2.

The most commonly reported adverse reactions (greater than or equal to 10%) associated with ILARIS treatment in TRAPS, HIDS/MKD, and FMF patients were injection-site reactions and nasopharyngitis. The reported adverse reactions (greater than or equal to 3%) associated with ILARIS treatment in TRAPS, HIDS/MKD, and FMF patients were injection-site reactions (10.1%), and infections, including nasopharyngitis (10.7%), upper respiratory tract infection (7.1%), rhinitis (5.3%), gastroenteritis (3.0%), and pharyngitis (3.0%). Serious infections (e.g., conjunctivitis, pneumonia, pharyngitis, pharyngotonsillitis) were observed in approximately 2.4% (0.03 per 100 patient-days) of patients receiving ILARIS in Part 2 of the TRAPS, HIDS/MKD, and FMF Study 1.

In the ILARIS treatment group, 1 TRAPS patient discontinued treatment due to adverse events, 2 HIDS/MKD patients discontinued treatment due to adverse events, and no FMF patients discontinued treatment due to an adverse event.

Injection-Site Reactions
In the TRAPS, HIDS/MKD, and FMF Study 1, subcutaneous injection-site reactions were observed in 10.1% of patients in Part 2 who had a mild or a moderate tolerability reaction. No severe injection-site reactions were reported and none led to discontinuation of treatment.

Adverse Reactions from Clinical Trials for Treatment of Still's Disease: SJIA and AOSD

The safety of ILARIS compared to placebo in SJIA patients was investigated in two Phase 3 studies *[see Clinical Studies (14.2)]*. Patients in SJIA Study 1 received a single dose of ILARIS 4 mg/kg (n = 43) or placebo (n = 41) via subcutaneous injection and were assessed at Day 15 for the efficacy endpoints and had a safety analysis up to Day 29. SJIA Study 2 was a two-part study with an open-label, single-arm active treatment period (Part I) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (Part II). Overall, 177 patients were enrolled into the study and received ILARIS 4 mg/kg (up to 300 mg maximum) in Part I, and 100 patients received ILARIS 4 mg/kg (up to 300 mg maximum) every 4 weeks or placebo in Part II. Adverse drug reactions listed in Table 2 showed higher rates than placebo from both trials. The adverse drug reactions associated with ILARIS treatment in greater than 10% of SJIA patients were infections, abdominal pain, and injection-site reactions. Serious infections (e.g., pneumonia, varicella, gastroenteritis, measles, sepsis, otitis media, sinusitis, adenovirus, lymph node abscess, pharyngitis) were observed in approximately 4% to 5% (0.02 to 0.17 per 100 patient-days) of patients receiving ILARIS in both studies.

Table 2: Tabulated Summary of Adverse Drug Reactions From Pivotal SJIA Clinical Trials

	SJIA Study 2			SJIA Study 1	
	Part I	Part II			
	ILARIS N = 177 n (%) (IR)^	ILARIS N = 50 n (%) (IR)	Placebo N = 50 n (%) (IR)	ILARIS N = 43 n (%) (IR)	Placebo N = 41 n (%) (IR)
Infections and infestations					
All infections (e.g., nasopharyngitis, [viral] upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)	97 (54.8%) (0.91)	27 (54%) (0.59)	19 (38%) (0.63)	13 (30.2%) (1.26)	5 (12.2%) (1.37)
Gastrointestinal disorders					
Abdominal pain (upper)	25 (14.1%) (0.16)	8 (16%) (0.15)	6 (12%) (0.08)	3 (7%) (0.25)	1 (2.4%) (0.23)
Skin and subcutaneous tissue disorders					
Injection-site reaction*					
mild	19 (10.7%)	6 (12.0%)	2 (4.0%)	0	3 (7.3%)
moderate	2 (1.1%)	1 (2.0%)	0	0	0

n = number of patients.
^IR = Exposure adjusted incidence rate per 100 patient-days.
*No injection-site reaction led to study discontinuation.

The safety profile of ILARIS in AOSD patients in a randomized, double-blind, placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Adverse Reactions from Clinical Trials for Treatment of Gout Flares

The safety of ILARIS compared to triamcinolone acetonide in patients with gout flares was assessed in four 12-week randomized, double-blind, active-controlled Phase 3 studies [see *Clinical Studies (14.4)* for details of the studies supporting efficacy] and in two 12-week double-blind active-controlled extension studies. In the ILARIS treatment groups 512 patients were treated up to 12 weeks and 165 of these patients up to 24 weeks. In the triamcinolone acetonide groups, 381 patients were treated up to 12 weeks and 152 of these patients up to 24 weeks. Patients received a single dose of ILARIS 150 mg (n = 467) via subcutaneous injection or triamcinolone acetonide 40 mg (n = 279) via intramuscular injection. Upon a new flare, 85 and 152 patients received at least one additional dose of ILARIS and triamcinolone acetonide, respectively.

The most commonly reported adverse drug reactions were infections and infestations (see Table 3). The most common infections reported in more than 2% of patients in the ILARIS treatment groups were nasopharyngitis, upper respiratory tract infections, and urinary tract infections. The trends observed in all infections are aligned with the overall known safety profile of canakinumab. Serious adverse events were reported in 1.4% of the ILARIS-treated patients, all of which were single events. No serious adverse events were reported in the triamcinolone acetonide-treated group.

Of the ILARIS-treated patients, 17% were 65 years of age and older, including 3% who were 75 years of age and older. No new safety findings were observed between these patients compared to patients under 65 years of age *[see Use in Specific Populations (8.5)*.

Table 3: Tabulated Summary of Adverse Drug Reactions From Pivotal Gout Flare Clinical Trials

System Organ Class Adverse reaction	**ILARIS 150 mg** *N = 552 n (%) (IR-w)	**Triamcinolone acetonide 40 mg** *N = 431 n (%) (IR-w)
Infections and infestations		
All infections (e.g., nasopharyngitis, upper respiratory tract infection, urinary tract infections)	90 (16.3%) (59.0)	40 (9.3%) (32.1)
Investigations		
Blood triglycerides increased	7 (1.3%) (3.8)	2 (0.5%) (1.3)
Platelet count decreased	4 (0.7%) (2.5)	1 (0.2%) (1.0)
Metabolism and nutrition disorders		
Hypertriglyceridemia	15 (2.7%) (9.5)	4 (0.9%) (3)
Musculoskeletal and connective tissue disorders		
Back pain	17 (3.1%) (10.9)	7 (1.6%) (6.2)
Nervous system disorders		
Dizziness	9 (1.6%) (5.8)	2 (0.5%) (1.7)

Abbreviation: SOC, system organ class.
*N = Number of patients at study entry.
IR-w = Study size weighted incidence rate (i.e., number of patients with an event per 100 patient-years).

Specific Adverse Reactions from Clinical Trials

Hypersensitivity

During clinical trials, no anaphylactic reactions attributable to treatment with canakinumab have been reported. In CAPS trials one patient discontinued and in TRAPS, HIDS/MKD, FMF, Still's disease, and gout trials no patients discontinued due to hypersensitivity reactions. ILARIS should not be administered to any patients with known clinical hypersensitivity to ILARIS *[see Contraindications (4)* and *Warnings and Precautions (5.3)]*.

Laboratory Abnormalities

- Hematology

TRAPS, HIDS/MKD, and FMF

Overall, in the TRAPS, HIDS/MKD, and FMF Study 1, neutrophil count decreased (greater than or equal to Grade 2) was reported in 6.5% of patients and platelet count decreased (greater than or equal to Grade 2) was reported in 0.6% of patients.

SJIA

During clinical trials with ILARIS, mean values decreased for white blood cells, neutrophils and platelets.

In the randomized, placebo-controlled portion of SJIA Study 2, decreased white blood cell counts (WBC) less than or equal to 0.8 times lower limit of normal (LLN) were reported in 5 patients (10.4%) in the ILARIS group compared to 2 patients (4.0%) in the placebo group. Transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/L were

reported in 3 patients (6.0%) in the ILARIS group compared to 1 patient (2.0%) in the placebo group. One case of ANC less than $0.5x10^9$/L was observed in the ILARIS group and none in the placebo group.

Mild (less than LLN and greater than 75 x 10^9/L) and transient decreases in platelet counts were observed in 3 (6.3%) ILARIS-treated patients versus 1 (2.0%) placebo-treated patient.

Gout Flares

In the pooled analysis of patients with gout flares from four 12-week randomized, double-blind, active-controlled Phase 3 studies and two 12-week active-controlled extension studies, transient cytopenias were observed. Leukopenia (WBC ≤ 0.8 x LLN) was reported in 6.4% of ILARIS-treated patients compared to 1.4% of triamcinolone acetonide-treated patients. Neutropenia (ANC < 0.9 x LLN) was reported in 15.9% of patients treated with ILARIS compared to 2.1% treated with triamcinolone acetonide. Thrombocytopenia (platelet counts < LLN) was observed in 16.3% of patients treated with ILARIS versus 12.5% of patients treated with triamcinolone acetonide.

- Uric Acid

Gout Flares

The proportion of patients with laboratory abnormalities (from normal at baseline to >ULN or from ≤9.9 mg/dl at baseline to > 9.9 mg/dl) and/or adverse reactions of increased uric acid levels were numerically higher in the ILARIS group (43.8% for ILARIS vs. 40.1% for (triamcinolone acetonide).

- Hepatic Transaminases

Elevations of transaminases (ALT/AST) have been observed in patients treated with ILARIS.

SJIA

In the randomized, placebo-controlled portion of SJIA Study 2, high ALT and/or AST ≥ 3 times upper limit of normal (ULN) were reported in 2 (4.1%) ILARIS-treated patients and 1 (2.0%) placebo patient. All patients had normal values at the next visit.

Gout Flares

In the randomized double-blind studies up to 24 weeks high ALT and AST ≥ 3 times upper limit of normal (ULN) were reported in 1.6% and 0.5% of ILARIS-treated patients respectively, and 2.6% and 1.9% of the triamcinolone acetonide-treated patients, respectively.

- Bilirubin

SJIA

Asymptomatic and mild elevations of serum bilirubin have been observed in patients treated with ILARIS without concomitant elevations of transaminases.

- Hypertriglyceridemia

Gout Flares

The proportion of patients with hypertriglyceridemia events in the randomized double-blind studies up to 24 weeks was higher in the ILARIS group compared to the triamcinolone acetonide-treated group (5.6% vs. 1.9%). The majority of abnormal values were noted at a single visit.

6.2 Immunogenicity

A biosensor binding assay or a bridging immunoassay was used to detect antibodies directed against canakinumab in patients who received ILARIS. Following treatment with ILARIS, antibodies against ILARIS were observed in approximately 1.4 %, 1.2%, and 3.5% of the patients with CAPS, SJIA, and gout flares, respectively. Neutralizing antibodies were detected in < 1% of patients with gout flares. No apparent correlation of antibody development to clinical response or adverse events was observed. The CAPS clinical studies employed the biosensor binding assay, most of the SJIA clinical studies employed the bridging assay, and the gout clinical studies used initially the biosensor assay and for later studies or extensions the bridging assay. The data obtained in an assay are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, comparison of the incidence of antibodies to canakinumab between the CAPS, SJIA, and gout flare clinical studies or with the incidence of antibodies to other products may be misleading.

No TRAPS, HIDS/MKD, FMF, SJIA, or AOSD patients treated with ILARIS doses of 150 mg and 300 mg over 16 weeks of treatment tested positive for anti-canakinumab antibodies.

7 DRUG INTERACTIONS

Interactions between ILARIS and other medicinal products have not been investigated in formal studies.

7.1 TNF-Blocker and IL-1 Blocking Agent

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors in another patient population. Use of ILARIS with TNF inhibitors may also result in similar toxicities and is not recommended because this may increase the risk of serious infections *[see Warnings and Precautions (5.1)]*.

The concomitant administration of ILARIS with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacological interactions between ILARIS and a recombinant IL-1ra, concomitant administration of ILARIS and other agents that block IL-1 or its receptors is not recommended.

7.2 Immunization

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving ILARIS. Therefore, avoid administration of live vaccines concurrently with ILARIS. It is recommended that, if possible, pediatric and adult patients complete all immunizations in accordance with current immunization guidelines prior to initiating ILARIS therapy *[see Warnings and Precautions (5.4)]*.

7.3 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus, it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed, and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data from postmarketing experience and published case reports on ILARIS use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, and adverse maternal or fetal outcomes. Canakinumab, like other monoclonal antibodies, is actively transported across the placenta mainly during the third trimester of pregnancy and may cause immunosuppression in the *in utero* exposed infant (*see Clinical Considerations*).

In an animal embryo-fetal development study with marmoset monkeys, there was no evidence of embryotoxicity or fetal malformations with subcutaneous administration of canakinumab during the period of organogenesis and later in gestation at doses that produced exposures approximately 11 times the exposure at the maximum recommended human dose (MRHD) and greater. Delays in fetal skeletal development were observed in marmoset monkeys following prenatal exposure to ILARIS at concentrations approximately 11 times the MRHD and greater. Similar delays in fetal skeletal development were observed in mice administered a murine analog of ILARIS during the period of organogenesis. Delays in skeletal ossification are changes from the expected ossification state in an otherwise normal structure/bone: these findings are generally reversible or transitory and not detrimental to postnatal survival *(see Animal Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Because IL-1 blockade may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants who were exposed to ILARIS *in utero* for at least 4 to 12 months following the mother's last dose of ILARIS. The ideal time to avoid live vaccines in infants exposed to ILARIS *in utero* is unknown, as there are insufficient data regarding infant serum levels of canakinumab at birth and the duration of persistence of canakinumab in infant serum after birth is also unknown.

Data

Animal Data

In an embryo-fetal development study, pregnant marmoset monkeys received canakinumab from gestation days 25 to 109 at doses that produced exposures approximately 11 times that achieved with MRHD and greater (on a plasma area under the curve [AUC] basis with maternal subcutaneous doses of 15, 50, or 150 mg/kg twice weekly). ILARIS did not elicit any evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since ILARIS does not cross-react with mouse or rat IL-1β, pregnant mice were subcutaneously administered a murine analog of ILARIS at doses of 15, 50, or 150 mg/kg during the period of organogenesis on gestation days 6, 11, and 17. The incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased in a dose-dependent manner at all dose levels tested.

8.2 Lactation

Risk Summary

There is no information regarding the presence of canakinumab in human milk or the effects on milk production. There are a small number of published case reports that do not establish an association between maternal canakinumab use during lactation and adverse effects on breastfed infants. Maternal IgG is known to be present in human milk. The effects of canakinumab in breast milk and possible systemic exposure in the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ILARIS and any potential adverse effects on the breastfed infant from ILARIS or from the underlying maternal condition.

8.4 Pediatric Use

The CAPS trials with ILARIS included a total of 23 pediatric patients with an age range from 4 years to 17 years (11 adolescents were treated subcutaneously with 150 mg, and 12 children were treated with 2 mg/kg based on body weight greater than or equal to 15 kg and less than or equal to 40 kg). The majority of patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g., Serum Amyloid A [SAA] and C-Reactive Protein). Overall, the efficacy and safety of ILARIS in pediatric and adult patients were comparable. Infections of the upper respiratory tract were the most frequently reported infection. The safety and effectiveness of ILARIS in CAPS patients less than 4 years of age has not been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

The safety and effectiveness of ILARIS in SJIA patients less than 2 years of age have not been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3)]*.

The TRAPS, HIDS/MKD, and FMF trial included a total of 102 pediatric patients (TRAPS, HIDS/MKD and FMF patients) with an age range from 2 to 17 years who received ILARIS. Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of ILARIS in pediatric patients compared to the overall TRAPS, HIDS/MKD, and FMF populations (comprised of adult and pediatric patients, N = 169). The majority of pediatric patients achieved improvement in clinical symptoms and objective markers of inflammation *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

The safety and effectiveness of ILARIS for the treatment of gout flares in the pediatric population have not been established.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ILARIS, pediatric patients receive all recommended vaccinations. Avoid use of live virus vaccines concurrently with ILARIS treatment in pediatric patients or in infants exposed *in utero* following maternal administration *[see Warnings and Precautions (5.4)* and *Use in Specific Populations (8.1)]*.

8.5 Geriatric Use

Clinical studies of ILARIS in patients with CAPS, TRAPS, HIDS/MKD, FMF and Still's disease, did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger patients.

In the clinical studies for gout flares, of the total number of ILARIS- treated patients (n=491), 85 (17.3 %) were 65 years of age and older, while 16 (3.3 %) were 75 years of age and older *[see Clinical Studies (14.4)]*. Overall, the efficacy profile of ILARIS in patients with gout flares was comparable between the age group of patients less than 65 years of age, and of patients 65 to 75 years of age. The studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently from younger patients. No new safety findings were observed in patients across these age groups *[see Adverse Reactions (6.1)*.

8.6 Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with renal impairment.

8.7 Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of ILARIS administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

No confirmed case of overdose has been reported. In the case of overdose, it is recommended that the subject be monitored for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment be instituted immediately.

11 DESCRIPTION

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298 (Asn 298).

The biological activity of canakinumab is measured by comparing its inhibition of IL-1β-dependent expression of the reporter gene luciferase to that of a canakinumab internal reference standard, using a stably transfected cell line.

ILARIS Injection

ILARIS (canakinumab) Injection is supplied as a sterile, preservative-free, clear to opalescent, colorless to slightly brownish-yellow solution for subcutaneous injection in a single-dose, glass vial with coated stopper and aluminum flip-off cap. Each vial delivers 1 mL containing 150 mg canakinumab, L-histidine (2.1 mg), L-histidine HCl monohydrate (1.3 mg), mannitol (49.2 mg), polysorbate 80 (0.4 mg), and Sterile Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Canakinumab is a human monoclonal anti-human IL-1β antibody of the IgG1/κ isotype. Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra).

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Autoinflammatory Syndrome-1 [CIAS1]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

The NLRP3 protein is an important component of the inflammasome and regulates the protease caspase-1 and controls the activation of IL-1β. Mutations in NLRP3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation. Still's disease is a severe autoinflammatory disease, driven by innate immunity by means of proinflammatory cytokines such as IL-1β.

Gout flares are characterized by activation of resident macrophages and infiltrating neutrophils in the joint, and concomitant overproduction of IL-1β resulting in an acute painful inflammatory response. IL-1β production by macrophages is triggered by uric acid (monosodium urate monohydrate) crystals in the joint and surrounding tissue through activation of the NLRP3 inflammasome complex.

12.2 Pharmacodynamics

C-reactive protein and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS and gout flares. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Following ILARIS treatment, CRP, and SAA levels normalize within 8 days.

In patients with gout flares, CRP and SAA were rapidly reduced following ILARIS treatment. Reductions in CRP and SAA were sustained throughout the 24-week observation period. Improvement in pharmacodynamic markers may not be representative of clinical response.

In SJIA the median percent reduction in CRP from baseline to Day 15 was 91%. Improvement in pharmacodynamic markers may not be representative of clinical response.

12.3 Pharmacokinetics

The pharmacokinetic properties of canakinumab are typical for an IgG-type antibody and are comparable in different diseases but influenced by body weight.

Absorption

The peak serum canakinumab concentration (C_{max}) of 16 ± 3.5 mcg/mL occurred approximately 7 days after subcutaneous administration of a single, 150 mg dose subcutaneously to adult CAPS patients. The mean terminal half-life was 26 days. The absolute bioavailability of subcutaneous canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion or from 150 to 300 mg as subcutaneous injection.

Distribution

Canakinumab binds to serum IL-1β. Canakinumab volume of distribution (V_{ss}) varied according to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg, 3.2 liters in a SJIA patient weighing 33 kg, and 6.34 liters for a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing 70 kg and 7.9 liters in a typical patient with gout flares of body weight 93 kg. The expected accumulation ratio was 1.3-fold for CAPS patients, 1.6-fold for SJIA patients, and 1.1-fold for patients with gout flares following 6 months of subcutaneous dosing of 150 mg ILARIS every 8 weeks, 4 mg/kg every 4 weeks, and 150 mg every 12 weeks, respectively.

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg, 0.11 L/day in an SJIA patient weighing 33 kg, and 0.17 L/day in a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing 70 kg and 0.23 L/day in a typical patient with gout flares of body weight 93 kg. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender- or age-related pharmacokinetic differences were observed after correction for body weight.

Pediatric Patients

Pharmacokinetic properties are similar in Periodic Fever Syndromes (CAPS, TRAPS, HIDS/MKD, FMF) and SJIA pediatric populations. In patients less than 2 years of age (n = 7), the exposure of canakinumab were comparable to older age groups with the same weight-based dose.

In CAPS patients, peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric patients. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

In SJIA, exposure parameters (such as AUC and C_{max}) were comparable across age groups from 2 years of age and above following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks. Across the indications, SJIA and AOSD, the pharmacokinetics of canakinumab are similar.

In TRAPS, HIDS/MKD, and FMF exposure parameter trough concentrations were comparable across age groups from 2 to less than 20 years following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab.

As canakinumab does not cross-react with rodent IL-1β, male and female fertility were evaluated in a mouse model using a murine analog of canakinumab. Male mice were treated weekly beginning 4 weeks prior to mating and continuing through 3 weeks after mating. Female mice were treated weekly for 2 weeks prior to mating through gestation day 3 or 4. The murine analog of canakinumab did not alter either male or female fertility parameters at subcutaneous doses up to 150 mg/kg.

14 CLINICAL STUDIES

14.1 Treatment of CAPS

The efficacy and safety of ILARIS for the treatment of CAPS was demonstrated in CAPS Study (NCT00465985), a 3-part trial in patients 9 to 74 years of age with the MWS phenotype of CAPS. Throughout the trial, patients weighing more than 40 kg received ILARIS 150 mg and patients weighing 15 to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received ILARIS. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week open-label active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and had serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10 mg/L. A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients one week following initiation of treatment and in 97% of patients by Week 8 (see Table 4 and Figure 1). In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared as compared to none (0%) of the patients randomized to ILARIS. The 95% confidence interval for treatment difference in the proportion of flares was 53% to 96%. At the end of Part 2, all 15 patients treated with ILARIS had absent or minimal disease activity and skin disease (see Table 4).

In a second trial (NCT00465985), patients 4 to 74 years of age with both MWS and FCAS phenotypes of CAPS were treated in an open-label manner. Treatment with ILARIS resulted in clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week.

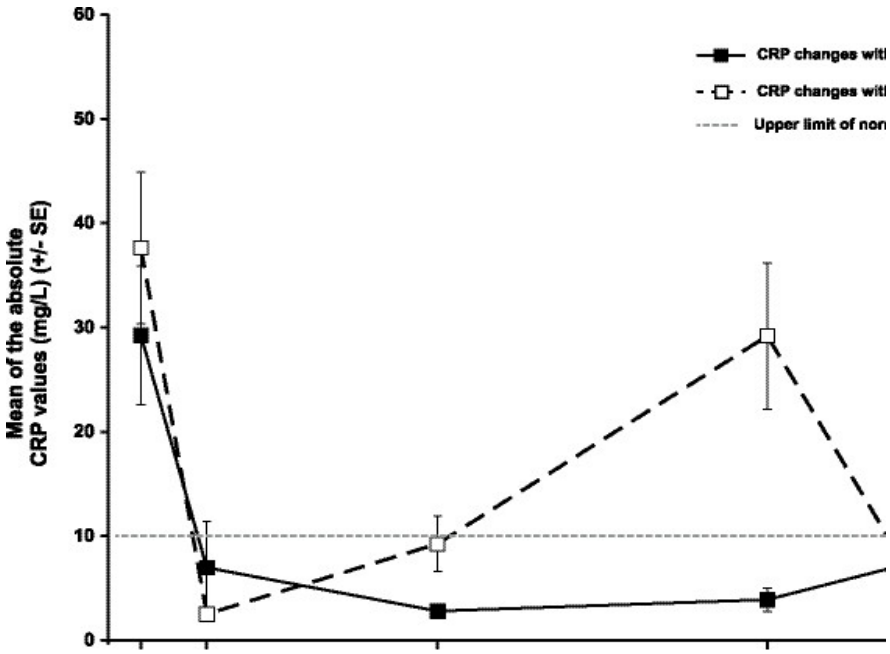
Table 4: Physician's Global Assessment of Auto Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part 2 (Using LOCF, ITT Population)

		ILARIS N = 15		Placebo N = 16	
	Baseline	Start of Part 2 (Week 8)	End of Part 2	Start of Part 2 (Week 8)	End of Part 2
Physician's Global Assessment of Auto Inflammatory Disease Activity – n (%)					
Absent	0/31 (0)	9/15 (60)	8/15 (53)	8/16 (50)	0/16 (0)
Minimal	1/31 (3)	4/15 (27)	7/15 (47)	8/16 (50)	4/16 (25)
Mild	7/31 (23)	2/15 (13)	0/15 (0)	0/16 (0)	8/16 (50)
Moderate	19/31 (61)	0/15 (0)	0/15 (0)	0/16 (0)	4/16 (25)
Severe	4/31 (13)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)
Assessment of skin disease – n (%)					
Absent	3/31 (10)	13/15 (87)	14/15 (93)	13/16 (81)	5/16 (31)
Minimal	6/31 (19)	2/15 (13)	1/15 (7)	3/16 (19)	3/16 (19)

		ILARIS N = 15		Placebo N = 16	
Mild	9/31 (29)	0/15 (0)	0/15 (0)	0/16 (0)	5/16 (31)
Moderate	12/31 (39)	0/15 (0)	0/15 (0)	0/16 (0)	3/16 (19)
Severe	1/32 (3)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

Markers of inflammation CRP and SAA normalized within 8 days of treatment in the majority of patients. Normal mean CRP (Figure 1) and SAA values were sustained throughout CAPS Study 1 in patients continuously treated with canakinumab. After withdrawal of canakinumab in Part 2, CRP (Figure 1) and SAA values again returned to abnormal values and subsequently normalized after reintroduction of canakinumab in Part 3. The pattern of normalization of CRP and SAA was similar.

Figure 1. Mean C-Reactive Protein Levels at the End of Parts 1, 2, and 3 of CAPS Study 1



14.2 Treatment of Periodic Fever Syndromes: TRAPS, HIDS/MKD, and FMF

The efficacy and safety of ILARIS for the treatment of TRAPS, HIDS/MKD, and FMF was demonstrated in a 4-Part study (TRAPS, HIDS/MKD, and FMF Study 1) (NCT02059291) consisting of three separate, disease cohorts (TRAPS, HIDS/MKD, and FMF) which enrolled 185 patients aged greater than 28 days. Patients in each cohort entered a 12-week screening period (Part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (Part 2) where they received either 150 mg ILARIS (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. Part 3 and Part 4 of this study are ongoing.

Randomized patients in Part 2 treated with ILARIS whose disease flare did not resolve, or who had persistent disease activity from Day 8 up to Day 14 (Physician's Global Assessment [PGA] greater than or equal to 2 or C-reactive Protein [CRP] greater than 10 mg/L and no reduction by at least 40% from baseline) received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). Patients treated with ILARIS whose disease flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 (PGA greater than or equal to 2 or CRP greater than 10 mg/L and no reduction by at least 70% from baseline), also received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). On or after Day 29, patients treated with ILARIS in Part 2 with PGA greater than or equal to 2 and CRP greater than or equal to 30 mg/L were also up-titrated. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients weighing less than or equal to 40 kg) every 4 weeks.

The primary efficacy endpoint of the randomized, 16-week treatment period (Part 2) was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. Resolution of the index disease flare

(initial flare at the time of the randomization) was defined at the Day 15 visit as a PGA Disease Activity score less than 2 ("minimal or no disease") and C-reactive Protein (CRP) within normal range (less than or equal to 10 mg/L) or reduction greater than or equal to 70% from baseline. The key signs and symptoms assessed in the PGA for each condition were the following: TRAPS: abdominal pain, skin rash, musculoskeletal pain, eye manifestations; HIDS/MKD: abdominal pain; lymphadenopathy, aphthous ulcers; FMF: abdominal pain, skin rash, chest pain, arthralgia/arthritis. A new flare was defined as a PGA score greater than or equal to 2 ("mild, moderate, or severe disease") and CRP greater to or equal than 30 mg/L. In the 16-week treatment period (Part 2), patients who needed dose escalation, who crossed over from placebo to ILARIS, or who discontinued from the study due to any reason prior to Week 16 were considered as non-responders.

Patients randomized in the TRAPS cohort (N = 46) were aged 2 to 76 years (median age at baseline: 15.5 years) and of this population, 57.8% did not have fever at baseline. Randomized TRAPS patients were those with chronic or recurrent disease activity defined as 6 flares per year (median number of flares per year: 9.0) with PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 112.5 mg/L). In the TRAPS cohort, 11/22 (50.0%) patients randomized to ILARIS 150 mg every 4 weeks received up-titration to 300 mg every 4 weeks during the 16-week treatment period, while 21/24 (87.5%) patients randomized to placebo crossed over to ILARIS.

Patients randomized in the HIDS/MKD cohort (N = 72) were aged 2 to 47 years (median age at baseline: 11.0 years) and of this population, 41.7% did not have fever at baseline. Randomized HIDS/MKD patients were those with a confirmed diagnosis of HIDS according to known genetic MVK/enzymatic (MKD) findings, and documented prior history of greater than or equal to 3 febrile acute flares within a 6-month period (median number of flares per year: 12.0) when not receiving prophylactic treatment and during the study, had active HIDS flares defined as PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 113.5 mg/L). In the HIDS/MKD cohort, 19/37 (51.4%) patients randomized to ILARIS 150 mg every 4 weeks received up-titration to 300 mg every 4 weeks during the 16-week treatment period, while 31/35 (88.6%) patients randomized to placebo crossed over to ILARIS.

Patients randomized in the FMF cohort (N = 63) were aged 2 to 69 years (median age at baseline: 18.0 years) and of this population, 76.2% did not have fever at baseline. Randomized FMF patients were those with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine. Patients had active disease defined as at least one flare per month (median number of flares per year: 18.0) and CRP greater than 10 mg/L (median CRP at baseline: 94.0 mg/L). Patients were allowed to continue their stable dose of colchicine without change. Of the 63 randomized patients, 55 (87.3%) were taking concomitant colchicine therapy on or after randomization. In the FMF cohort, 10/31 (32.3%) patients randomized to ILARIS 150 mg every 4 weeks received up-titration to 300 mg every 4 weeks during the 16-week treatment period, while 27/32 (84.4%) patients randomized to placebo crossed over to ILARIS.

For the primary efficacy endpoint, ILARIS was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment from the time of the resolution of the index flare (see Table 5).

Table 5: Proportion of TRAPS, HIDS/MKD, and FMF Patients Who Achieved a Complete Response (Resolution of Index Flare by Day 15 and Maintained Through Week 16)

	ILARIS 150 mg	**Placebo**	**Treatment comparison**	
Cohort	**n/N (%)**	**n/N (%)**	**Odds ratio 95% CI**	**p-value**
TRAPS	10/22 (45.5%)	2/24 (8.3%)	9.17 (1.51, 94.61)	0.005
HIDS/MKD	13/37 (35.1%)	2/35 (5.7%)	8.94 (1.72, 86.41)	0.002
FMF	19/31 (61.3%)	2/32 (6.3%)	23.75 (4.38, 227.53)	<0.0001

Abbreviation: CI, confidence interval.
n = number of patients with the response.
N = number of patients evaluated for that response in each cohort.

At Day 15, a higher proportion of ILARIS-treated patients compared to placebo-treated patients experienced resolution of their index flare in all disease cohorts (see Table 6).

Table 6: Resolution of Index Flare (Full Analysis Set)

Resolution at Day 15*		
	ILARIS 150 mg every 4 weeks	**Placebo**
Variable	**n/N (%)**	**n/N (%)**
TRAPS	14/22 (63.6%)	5/24 (20.8%)
HIDS/MKD	24/37 (64.9%)	13/35 (37.1%)
FMF	25/31 (80.7%)	10/32 (31.3%)

n = number of patients with the response.

N = number of patients evaluated for that response in each cohort.

*Resolution of index disease flare (PGA less than 2 and CRP less than or equal to 10 mg/L or reduction greater than or equal to 70% from baseline).

There was supportive evidence of efficacy for ILARIS at Day 15, as compared to placebo, for the components of the primary endpoint, CRP and PGA Disease Activity score, as well as for the secondary endpoint SAA level (see Table 7).

Table 7: Proportion of TRAPS, HIDS/MKD, and FMF Patients Achieving PGA Less Than 2, CRP Less Than or Equal to 10 mg/L and SAA Less Than or Equal to 10 mg/L at Day 15*

	TRAPS			**HIDS/MKD**			**FMF**		
Variable	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**	**ILARIS 150 mg**	**Placebo**	**Treatment comparison**
	n/N (%)	**n/N (%)**	**Odds ratio 95% CI**	**n/N (%)**	**n/N (%)**	**Odds ratio 95% CI**	**n/N (%)**	**n/N (%)**	**Odds ratio 95% CI**
PGA less than 2	14/22 (63.6%)	8/24 (33.3%)	4.06 (1.12, 14.72)	26/37 (70.3%)	14/35 (40.0%)	3.42 (1.28, 9.16)	27/31 (87.1%)	13/32 (40.6%)	10.07 (2.78, 36.49)
CRP less than or equal to 10 mg/L	13/22 (59.1%)	8/24 (33.3%)	3.88 (1.05, 14.26)	25/37 (67.6%)	9/35 (25.7%)	6.05 (2.14, 17.12)	28/31 (90.3%)	9/32 (28.1%)	22.51 (5.41, 93.62)
SAA less than or equal to 10 mg/L	7/22 (31.8%)	2/24 (8.3%)	5.06 (0.92, 27.91)	10/37 (27.0%)	4/35 (11.4%)	2.94 (0.82, 10.53)	13/31 (41.9%)	5/32 (15.6%)	3.73 (1.11, 12.52)

Abbreviation: CI: confidence interval.

n = number of patients with the response.

N = number of patients evaluated for that response in each cohort. *ILARIS-treated patients who up-titrated or discontinued prior to Day 15 and placebo-treated patients who switched over to ILARIS or discontinued prior to Day 15 were classified as nonresponders.

14.3 Treatment of Still's Disease: AOSD and SJIA

SJIA

The efficacy of ILARIS for the treatment of active SJIA was assessed in 2 Phase 3 studies (SJIA Study 1 and SJIA Study 2). Patients enrolled were aged 2 to less than 20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of SJIA at least 2 months before enrollment (mean disease duration at baseline: 3.5 years). Patients had active disease defined as greater than or equal to 2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature greater than 38°C) for at least 1 day within 1 week before study drug administration, and CRP greater than 30 mg/L (normal range less than 10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in SJIA Study 2 (see below).

SJIA Study 1 (NCT00886769) was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short-term efficacy of ILARIS in 84 patients randomized to receive a single subcutaneous dose of 4 mg/kg ILARIS or

placebo (43 patients received ILARIS and 41 patients received placebo). The primary objective of this study was to demonstrate the superiority of ILARIS versus placebo in the proportion of patients who achieved at least 30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion which included both the pediatric ACR core set (ACR30 response) and absence of fever (temperature less than or equal to 38°C in the preceding 7 days) at Day 15.

Pediatric ACR responses are defined by achieving levels of percentage improvement (30%, 50%, and 70%) from baseline in at least 3 of the 6 core outcome variables, with worsening of greater than or equal to 30% in no more than one of the remaining variables. Core outcome variables included a physician global assessment of disease activity, parent or patient global assessment of well-being, number of joints with active arthritis, number of joints with limited range of motion, CRP, and functional ability (Childhood Health Assessment Questionnaire-CHAQ).

Percentages of patients by pediatric ACR response are presented in Table 8.

Table 8: Pediatric ACR Response at Days 15 and 29

	Day 15			Day 29		
	ILARIS N = 43	Placebo N = 41	Weighted Difference[1] (95% CI)[2]	ILARIS N = 43	Placebo N = 41	Weighted difference[1] (95% CI)[2]
ACR30	84%	10%	70% (56%, 84%)	81%	10%	70% (56%, 84%)
ACR50	67%	5%	65% (50%, 80%)	79%	5%	76% (63%, 88%)
ACR70	60%	2%	64% (49%, 79%)	67%	2%	67% (52%, 81%)

[1]Weighted difference is the difference between the ILARIS and placebo response rates, adjusted for the stratification factors (number of active joints, previous response to anakinra, and level of oral corticosteroid use).
[2]CI = confidence interval for the weighted difference.
N = Number of patients.

Results for the components of the pediatric ACR core set were consistent with the overall ACR response results, for systemic and arthritic components, including the reduction in the total number of active joints and joints with limited range of motion. Among the patients who returned for a Day 15 visit, the mean change in patient pain score (0 to 100 mm visual analogue scale) was -50.0 mm on ILARIS (N = 43), as compared to +4.5 mm on placebo (N = 25). The mean change in pain score among ILARIS-treated patients was consistent through Day 29. All patients treated with ILARIS had no fever at Day 3 compared to 87% of patients treated with placebo.

SJIA Study 2 (NCT00889863) was a randomized, double-blind, placebo-controlled, withdrawal study of flare prevention by ILARIS in patients with active SJIA. Flare was defined by worsening of greater than or equal to 30% in at least 3 of the 6 core Pediatric ACR response variables combined with improvement of greater than or equal to 30% in no more than 1 of the 6 variables, or reappearance of fever not due to infection for at least 2 consecutive days. The study consisted of 2 major parts: 177 patients were enrolled in the study and received 4 mg/kg ILARIS subcutaneously every 4 weeks in Part I and 100 of these patients continued into Part II to receive either ILARIS 4 mg/kg or placebo subcutaneously every 4 weeks.

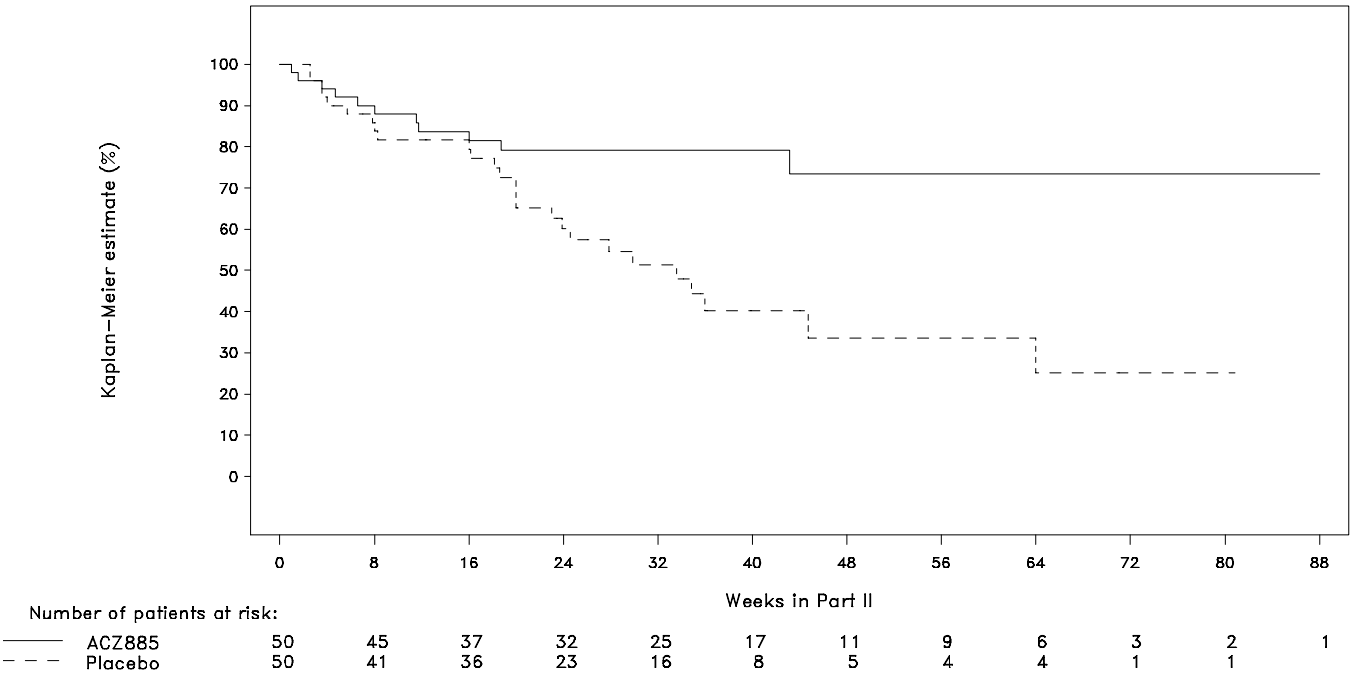
Corticosteroid Dose Tapering

Of the total 128 patients taking corticosteroids who entered the open-label portion of Study 2, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to Flare

Part II was a randomized withdrawal design to demonstrate that the time to flare was longer with ILARIS than with placebo. Follow-up stopped when 37 events had been observed resulting in patients being followed for different lengths of time. The probability of experiencing a flare over time in Part II was statistically lower for the ILARIS treatment group than for the placebo group (Figure 2). This corresponded to a 64% relative reduction in the risk of flare for patients in the ILARIS group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).

Figure 2. Kaplan-Meier Estimates of the Probability to Stay Flare-Free in Part II of SJIA Study 2 by Treatment (ILARIS (ACZ885) and Placebo groups)



Very few patients were followed for more than 48 weeks.

AOSD

The efficacy of ILARIS in adults with AOSD is based on the pharmacokinetic exposure and extrapolation of the established efficacy of ILARIS in SJIA patients. Efficacy of ILARIS was also assessed in a randomized, double-blind, placebo-controlled study that enrolled 36 patients (22 to 70 years old) diagnosed with AOSD. The efficacy data were generally consistent with the results of a pooled efficacy analysis of SJIA patients.

14.4 Treatment of Gout Flares

The efficacy of ILARIS was demonstrated in two 12-week, randomized, double-blind, active-controlled studies in patients with gout flares for whom NSAIDs and/or colchicine were contraindicated, not tolerated or ineffective, and who had experienced at least three gout flares in the previous year (Studies 1 and 2). The studies continued in 1) two 12-week, double-blind, active-controlled extensions, followed by 2) two open-label extensions and continued 3) in a third open-label extension (combined for both studies) up to a maximum of 36 months where all patients were treated with ILARIS upon a new flare.

In Study 1 (NCT01029652), patients were randomized to receive ILARIS 150 mg subcutaneous (N = 115) or triamcinolone acetonide 40 mg intramuscular (N = 115) at baseline and thereafter treated upon a new flare. Two patients randomized to canakinumab were not included in the analysis as they did not receive any study medication. In Study 2 (NCT01080131), patients were randomized to receive ILARIS 150 mg subcutaneous (N =112) or triamcinolone acetonide 40 mg intramuscular (N =114) at baseline and thereafter treated upon a new flare.

In Studies 1 and 2, over 85% of patients had at least one co-morbidity, including hypertension (60%), obesity (53%), diabetes (15%), and ischemic heart disease (12%). Twenty-five percent of patients had chronic kidney disease (stage ≥3), based on eGFR. Concomitant treatment with allopurinol or other uric acid lowering therapies was reported by 42% of patients at entry.

The majority of patients (73%) reported between 3-6 flares in the year prior to study entry and the remainder reported seven or more flares. Approximately one-third of the patients enrolled [76 in the ILARIS group (33.5%) and 84 in the triamcinolone acetonide (36.7%) group] had documented inability (intolerance, contraindication or lack of response) to use both, NSAIDs and colchicine. The remainder had intolerance, contraindication or lack of response to either NSAIDs or colchicine.

In both studies, the co-primary endpoints were: (i) patient's assessment of gout flare pain intensity at the most affected joint at 72 hours post-dose measured on a 0-100 mm visual analogue scale (VAS) and (ii) the time to first new gout flare. The studies aimed to determine whether ILARIS 150 mg would be superior to triamcinolone acetonide 40 mg.

Study 3 (NCT01356602), an additional 12-week, randomized, double-blind, active-controlled study, enrolled 397 patients with ILARIS 150 mg subcutaneous (Pre-Filled Syringe (PFS), N=133, Lyophilizate (LYO), N=132) or triamcinolone acetonide 40 mg intramuscular (N=132). Eight patients (2 ILARIS PFS, 3 ILARIS LYO, 3 triamcinolone) were not included for efficacy assessment as they did not receive study medication. Pain intensity at the most affected joint, assessed on a 0-100 mm VAS at 72-hours post-dose was the primary endpoint, and time to first new gout flare was a secondary endpoint. Approximately 44% of patients (45.9% ILARIS PFS group, 47.4%, ILARIS LYO group and 40.6% in the triamcinolone acetonide group) were unable to use NSAIDs and colchicine (due to contraindications, intolerance, or inadequate response) in this study.

Analyses of both endpoints were conducted for Studies 1, 2, and 3 for the subpopulation of patients unable to use NSAIDs and colchicine (due to contraindications, intolerance, or inadequate response) and overall population of patients unable to use NSAIDs and/or colchicine.

Efficacy on Pain

In all studies (Study 1, 2, and 3), pain intensity of the most affected joint (0-100 mm VAS) at 72 hours post-dose was consistently lower for patients treated with ILARIS compared with triamcinolone acetonide in the subpopulation of patients unable to use NSAIDs and colchicine as shown in Table 9, and Figure 3 (Study 3). This benefit of ILARIS on pain intensity was comparable to the overall patient populations i.e., patients unable to use NSAIDs and/or colchicine in all three studies (see Table 9).

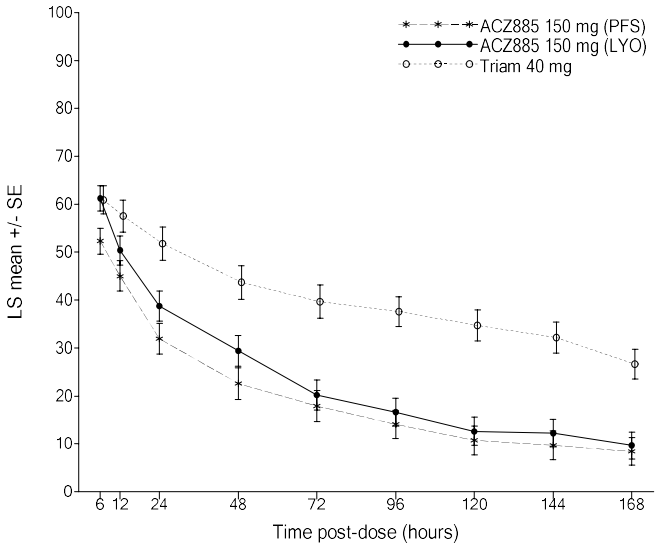
Table 9: Pain Intensity of the Most Affected Joint at 72-h post treatment

Study	**Population**	**ILARIS 150 mg**		**Triamcinolone acetonide 40mg**		**Difference (95% CI)* in Pain Intensity 72 Hours Post-dose VAS (0-100 mm): ILARIS vs. Triamcinolone acetonide**
		N	**Mean (SE)***	**N**	**Mean (SE)***	
Study 1	Patients unable to use NSAIDs and colchicine	22	21.4 (6.05)	37	38.4 (4.65)	-17.0 mm (-32.3, -1.6)
	Patients unable to use NSAIDs and/or colchicine	113	27.9 (2.42)	115	39.7 (2.40)	-11.8 mm (-18.5, -5.1)
Study 2	Patients unable to use NSAIDs and colchicine	53	24.1 (3.32)	44	33.1 (3.65)	-9.1 mm (-18.9, 0.8)
	Patients unable to use NSAIDs and/or colchicine	112	21.9 (2.31)	114	31.7 (2.29)	-9.8 mm (-16.2, -3.4)
Study 3	Patients unable to use NSAIDs and colchicine	62	20.8 (3.11)	51	40.3 (3.42)	-19.5 mm (-28.6, -10.3)
		60[#]	18.5 (3.16)			-21.8 mm (-31.0, -12.6)
	Patients unable to use NSAIDs and/or colchicine	129	19.7 (2.05)	129	32.4 (2.05)	-12.7 mm (-18.4, -7.0)
		131[#]	17.0 (2.04)			-15.4 mm (-21.1, -9.8)

Abbreviation: CI = confidence interval; SE=Standard Error

Prefilled Syringe (PFS) formulation.
* Adjusted mean, standard error for mean and difference between treatment groups are estimated based on analysis of covariance (ANCOVA) model with treatment, baseline VAS score and baseline BMI as covariates. For Study 3, the use of urate lowering therapy (Yes/No) at baseline is also included in the model as additional covariate.
N = number of patients randomized and received at least one dose of study treatment.

Figure 3. Pain Intensity Over Time in the Subpopulation of Patients Unable to Use NSAIDs and Colchicine (Study 3, ILARIS (ACZ885) 150mg)



Time to New Flare

In the subpopulation of patients in Studies 1, 2 and 3 unable to use NSAIDs and colchicine, time to new flare over 12 weeks from randomization showed a reduction in the risk of a new flare when treated with ILARIS compared with triamcinolone acetonide 40 mg (see Table 10). This risk reduction for a new flare after ILARIS treatment versus triamcinolone acetonide was comparable to the overall patient population over 12 weeks in all 3 studies (see Table 10).

Table 10: Time to New Flare Over the 12 Weeks From Randomization

Study	Population	ILARIS 150 mg		Triamcinolone acetonide 40mg		Risk reduction for a new flare ILARIS vs. Triamcinolone acetonide Hazard ratio[#] (95% CI)
		N	Flare rate*(n)	N	Flare rate*(n)	
Study 1	Patients unable to use NSAIDs and colchicine	22	14% (3)	38	46% (17)	75% 0.25 (0.07, 0.85)
	Patients unable to use NSAIDs and/or colchicine	113	19% (21)	115	37% (40)	55 % 0.45 (0.26 to 0.76)
Study 2	Patients unable to use NSAIDs and colchicine	54	16% (8)	46	43% (19)	72% 0.28 (0.12, 0.65)
	Patients unable to use NSAIDs and/or colchicine	112	14% (15)	114	38% (42)	68% 0.32 (0.18 to 0.58)
Study 3	Patients unable to use NSAIDs and colchicine	62	10% (6)	51	32% (15)	71% 0.29 (0.11, 0.74)
		60[#]	3% (2)			91% 0.09 (0.02, 0.41)
	Patients unable to use NSAIDs and/or colchicine	129	10% (12)	129	44% (52)	82% 0.18 (0.10, 0.34)
		131[#]	9% (12)			83% 0.17 (0.09, 0.33)

Abbreviation: CI = confidence interval.
Prefilled Syringe (PFS) formulation.
* Flare rates up to 12 weeks are estimated using Kaplan-Meier method; n = number of patients with new flares. The risk reduction and hazard ratio between treatment groups are estimated using Cox proportional hazard (Cox-PH) model with treatment and baseline BMI as covariates. For study 3, the use of urate lowering therapy (Yes/No) at baseline is also included in the model as additional covariate.
N = number of patients randomized and received at least one dose of study treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ILARIS Injection (Solution)

Carton of 1 vial…….NDC 0078-0734-61

Each single-dose vial of ILARIS (canakinumab) Injection delivers 150 mg/mL sterile, preservative-free, clear to slightly opalescent, colorless to a slight brownish to yellow solution.

Storage and Handling The unopened vial must be stored refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Store in the original carton to protect from light. Do not use beyond the date stamped on the label. ILARIS does not contain preservatives. Discard any unused portions of ILARIS or waste material in accordance with local requirements.

Keep this and all drugs out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise the patient of the potential benefits and risks of ILARIS. Physicians should instruct their patients to read the Medication Guide before starting ILARIS therapy.

Drug Administration

Advise the patient that healthcare providers should perform administration of ILARIS by the subcutaneous injection route *[see Dosage and Administration (2.1)]*.

Infections

Caution the patient that ILARIS use has been associated with serious infections. Counsel the patient to contact their healthcare professional immediately if they develop an infection after starting ILARIS. Treatment with ILARIS should be discontinued if a patient develops a serious infection. Counsel the patient not to take any IL-1 blocking drug, including ILARIS, if they are also taking a drug that blocks TNF, such as etanercept, infliximab, or adalimumab. Use of ILARIS with other IL-1 blocking agents, such as rilonacept and anakinra is not recommended. Caution the patient not to receive ILARIS if they have a chronic or active infection, including HIV, Hepatitis B, or Hepatitis C *[see Warnings and Precautions (5.1)]*.

Vaccinations

Prior to initiation of therapy with ILARIS, physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ILARIS *[see Warnings and Precautions (5.4)]*.

Injection-Site Reactions

Physicians should explain to patients that a very small number of patients in the clinical trials experienced a reaction at the subcutaneous injection site. Injection-site reactions may include pain, erythema, swelling, pruritus, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Healthcare providers should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Hypersensitivity

Counsel the patient to contact their healthcare provider immediately if they develop signs of allergic reaction, such as difficulty breathing or swallowing, nausea, dizziness, skin rash, itching, hives, palpitations, or low blood pressure *[see Warnings and Precautions (5.3)]*.

Pregnancy

Advise female patients of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

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Medication Guide

ILARIS® (i-LAHR-us)

(canakinumab)

injection, for subcutaneous use

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

ILARIS can cause serious side effects, including:

- **Increased risk of serious infections.** ILARIS can lower the ability of your immune system to fight infections. Your healthcare provider should:
  - test you for tuberculosis (TB) before you receive ILARIS.
  - monitor you closely for symptoms of TB during treatment with ILARIS.
  - check you for symptoms of any type of infection before, during, and after your treatment with ILARIS.

Tell your healthcare provider right away if you have any symptoms of an infection, such as fever, sweats or chills, cough, flu-like symptoms, weight loss, shortness of breath, blood in your phlegm, sores on your body, warm or painful areas on your body, diarrhea or stomach pain, or feeling very tired.

See **"What are possible side effects of ILARIS?"** for more information about side effects.

What is ILARIS?

ILARIS is a prescription medicine injected by your healthcare provider just below the skin (subcutaneous) used to treat:

- The following Periodic Fever Syndromes:
  - Adults and children 4 years of age and older who have auto-inflammatory diseases called Cryopyrin-Associated Periodic Syndromes (CAPS), including:
    - Familial Cold Auto-inflammatory Syndrome (FCAS).
    - Muckle-Wells Syndrome (MWS).
  - Adults and children who have an auto-inflammatory disease called Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).
  - Adults and children who have an auto-inflammatory disease called Hyperimmunoglobulin D Syndrome (HIDS) (also known as Mevalonate Kinase Deficiency (MKD).
  - Adults and children who have an auto-inflammatory disease called Familial Mediterranean Fever (FMF).
- Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in children 2 years of age and older.
- Gout flares in adults who:
  - are not able to receive or tolerate treatment with non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine.
  - have not responded to treatment with NSAIDS and colchicine.
  - are not able to receive repeated treatment with steroids.

It is not known if ILARIS is safe and effective when used to treat:

- SJIA in children under 2 years of age.
- CAPS in children under 4 years of age.
- gout flares in children.

Who should not receive ILARIS?

- Do not receive ILARIS if you are allergic to canakinumab or any of the ingredients in ILARIS. See the end of this Medication Guide for a complete list of ingredients in ILARIS.

Before you receive ILARIS, tell your healthcare provider about all your medical conditions, including if you:

- think you have or are being treated for an active infection.
- have symptoms of an infection.
- have a history of infections that keep coming back.
- have a history of low white blood cells.
- have or have had HIV, Hepatitis B, or Hepatitis C.
- have recently received or are scheduled to receive any vaccinations.
  - You should be brought up to date with all age required vaccines before starting treatment with ILARIS.

- You should not receive 'live' vaccines while you are being treated with ILARIS and until your healthcare provider tells you that your immune system is no longer weakened.
- are pregnant or planning to become pregnant. It is not known if ILARIS will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving ILARIS.
- received ILARIS while you were pregnant. It is important that you tell your baby's healthcare provider before any vaccinations are given to your baby within 4 to 12 months after you received your last dose of ILARIS before giving birth.
- are breastfeeding or planning to breastfeed. It is not known if ILARIS passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive ILARIS.

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

- medicines that affect your immune system.
- medicines called IL-1 blocking agents, such as Kineret® (anakinra), Arcalyst® (rilonacept).
- medicines called Tumor Necrosis Factor (TNF) inhibitors, such as Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Simponi® (golimumab), or Cimzia® (certolizumab pegol).
- medicines that affect enzyme metabolism.

Ask your healthcare provider for a list of these medicines if you are not sure.

How should I receive ILARIS?

- ILARIS is given by your healthcare provider as an injection under the skin (subcutaneous injection):
  - every 8 weeks for CAPS.
  - every 4 weeks for TRAPS, HIDS/MKD, FMF, AOSD, and SJIA.
  - as a single dose at the time of a gout flares. If you have a new flare and need another dose of ILARIS, you must wait at least 12 weeks before receiving the next dose.

What are the possible side effects of ILARIS?

ILARIS can cause serious side effects, including:

- See **"What is the most important information I should know about ILARIS?"**
- **decreased ability of your body to fight infections (immunosuppression).** For people treated with medicines that cause immunosuppression like ILARIS, the chances of getting cancer may increase.
- **allergic reactions.** Allergic reactions can happen while you are receiving ILARIS. Call your healthcare provider right away if you have any of these symptoms of an allergic reaction:
  - difficulty breathing or swallowing
  - nausea
  - dizziness or feeling faint
  - rash
  - itching or hives
  - palpitations (feels like your heart is racing)
  - low blood pressure
- **risk of infection with live vaccines.** You should not get live vaccines if you are receiving ILARIS. Tell your healthcare provider if you are scheduled to receive any vaccines.

The most common side effects of ILARIS include:

When ILARIS is used for the treatment of CAPS:

- cold symptoms
- diarrhea
- flu (influenza)
- runny nose
- headache
- cough
- body aches
- nausea, vomiting, and diarrhea (gastroenteritis)
- feeling like you are spinning (vertigo)
- weight gain
- injection-site reactions (such as redness, swelling, warmth, or itching)
- nausea

When ILARIS is used for the treatment of TRAPS, HIDS/MKD, and FMF:

- cold symptoms
- upper respiratory tract infection
- runny nose
- sore throat
- nausea, vomiting, and diarrhea (gastroenteritis)
- injection-site reactions (such as redness, swelling, warmth, or itching)

When ILARIS is used for the treatment of Still's disease (AOSD and SJIA):

- cold symptoms
- runny nose
- nausea, vomiting, and diarrhea (gastroenteritis)
- upper respiratory tract infection
- sore throat
- stomach pain
- pneumonia
- urinary tract infection
- injection-site reactions (such as redness, swelling, warmth, or itching)

When ILARIS is used for the treatment of gout flares:

- cold symptoms
- urinary tract infection
- upper respiratory tract infection
- increased levels of triglycerides in the blood
- back pain

Tell your healthcare provider about any side effect that bothers you or does not go away.

These are not all the possible side effects of ILARIS. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ILARIS.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. You can ask your healthcare provider or pharmacist for information about ILARIS that was written for health professionals.

What are the ingredients in ILARIS?

Active ingredient: canakinumab.

Inactive ingredients: Solution for Injection: L-histidine, L-histidine HCl monohydrate, mannitol, polysorbate 80, sterile water for injection.

What are Periodic Fever Syndromes?

Periodic Fever Syndromes is the name for several different autoinflammatory diseases, including CAPS, TRAPS, HIDS/MKD, and FMF. People with these diseases cannot keep certain chemicals made by their body (interleukin-1 beta, also called IL-1β) at the correct level. All these diseases have symptoms that often come and go, with irritated body parts (inflammation) and elevated body temperature (fever). These conditions have a dysregulation of IL-1β production and share similar clinical features of recurrent episodes of inflammation and fever, such as rash, headache, pain (mostly in the joints, belly, eyes, muscles), fatigue, inflammation of other organs, such as heart, lungs, spleen, and brain.

What is Still's Disease (AOSD and SJIA)?

Still's disease (which is referred to as AOSD in adults and SJIA in children) is an autoinflammatory disorder which can be caused by having too much or being too sensitive to certain proteins, including interleukin-1 beta (IL-1β), and can lead to symptoms such as fever, rash, headache, feeling very tired (fatigue), or painful joints and muscles.

What is Gout Flare?

A gout flare is caused when a chemical called urate builds-up in the body, and needle-shaped crystals form in and around the joint. These crystals lead to inflammation with excessive production of certain proteins, such as interleukin-1 beta (also called IL-1β), which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint.

What is Macrophage Activation Syndrome (MAS)?

MAS is a syndrome associated with Still's disease and some other autoinflammatory diseases like HIDS/MKD that can lead to death. Tell your healthcare provider right away if your AOSD or SJIA symptoms get worse or if you have any of these symptoms of an infection:

- a fever lasting longer than 3 days.
- a cough that does not go away.
- redness in one part of your body.
- warm feeling or swelling of your skin.

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East Hanover, New Jersey 07936

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For more information about ILARIS, call 1-877-452-7471 or visit www.ILARIS.com.

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 8/2023

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

After reconstitution, each ml of solution contains 150 mg canakinumab.

* human monoclonal antibody produced in mouse myeloma Sp2/0 cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

The powder is white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Periodic fever syndromes

Ilaris is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:

Cryopyrin-associated periodic syndromes
Ilaris is indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including:

- Muckle-Wells syndrome (MWS),
- Neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular syndrome (CINCA),
- Severe forms of familial cold autoinflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS)
Ilaris is indicated for the treatment of tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)
Ilaris is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Familial Mediterranean fever (FMF)
Ilaris is indicated for the treatment of Familial Mediterranean Fever (FMF). Ilaris should be given in combination with colchicine, if appropriate.

Ilaris is also indicated for the treatment of:

Still's disease

Ilaris is indicated for the treatment of active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

Gouty arthritis

Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (see section 5.1).

4.2 Posology and method of administration

For CAPS, TRAPS, HIDS/MKD, FMF and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

Posology

CAPS: Adults, adolescents and children aged 2 years and older
The recommended starting dose of canakinumab for CAPS patients is:
Adults, adolescents and children ≥ 4 years of age:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
- 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg

Children 2 to < 4 years of age:

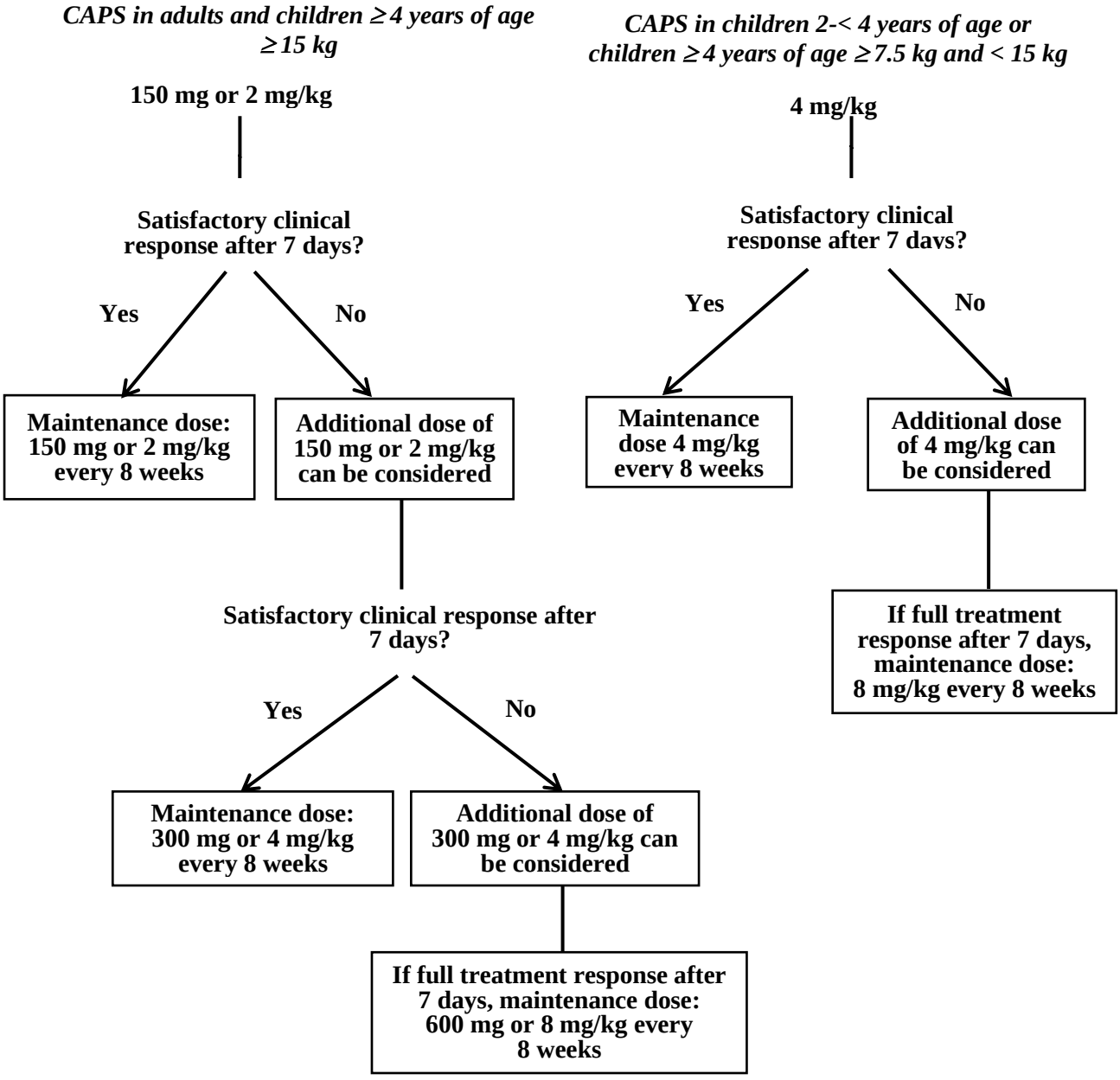
- 4 mg/kg for patients with body weight ≥ 7.5 kg

This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of canakinumab at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited.



TRAPS, HIDS/MKD and FMF: Adults, adolescents and children aged 2 years and older

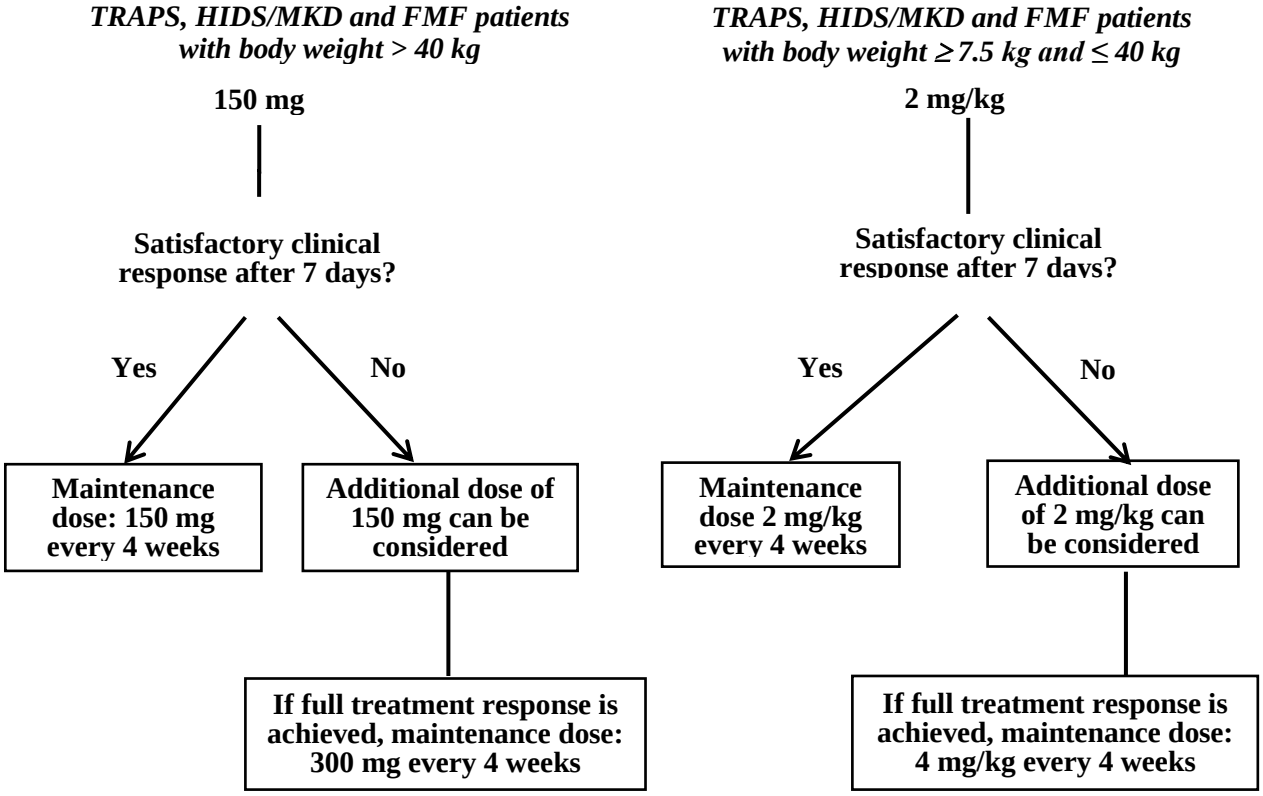
The recommended starting dose of canakinumab in TRAPS, HIDS/MKD and FMF patients is:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 7.5 kg and ≤ 40 kg

This is administered every four weeks as a single dose via subcutaneous injection.

If a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained.

Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.



Still's disease (SJIA and AOSD)
The recommended dose of canakinumab for patients with Still's disease with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis
Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Canakinumab should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of canakinumab for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with canakinumab. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered (see section 5.2).

Special populations

Paediatric population
CAPS, TRAPS, HIDS/MKD and FMF
The safety and efficacy of canakinumab in CAPS, TRAPS, HIDS/MKD and FMF patients under 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

SJIA
The safety and efficacy of canakinumab in SJIA patients under 2 years of age have not been established. No data are available.

Gouty arthritis
There is no relevant use of canakinumab in the paediatric population in the indication gouty arthritis.

Elderly
No dose adjustment is required.

Hepatic impairment
Canakinumab has not been studied in patients with hepatic impairment. No recommendation on a posology can be made.

Renal impairment
No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited.

Method of administration

For subcutaneous use.
The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. It is recommended to select a different injection site each time the product is injected to avoid soreness. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar tissue should be avoided as this may result in insufficient exposure to canakinumab.

Each vial is for single use in a single patient, for a single dose.

After proper training in the correct injection technique, patients or their caregivers may inject canakinumab if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

For instructions on reconstitution 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.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Canakinumab is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with canakinumab. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.

Treatment of CAPS, TRAPS, HIDS/MKD, FMF and Still's disease (SJIA and AOSD)
Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis
Canakinumab should not be administered during an active infection.
Concomitant use of canakinumab with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during canakinumab treatment. The causal relationship of canakinumab to these events cannot be excluded.

Tuberculosis screening

In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with canakinumab without clinical evidence of a latent or active tuberculosis infection.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as canakinumab increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay or chest X-ray) should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with canakinumab. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during canakinumab therapy. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including canakinumab. Treatment with canakinumab should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies

Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions

Hypersensitivity reactions with canakinumab therapy have been reported. The majority of these events were mild in severity. During clinical development of canakinumab in over 2,600 patients, no anaphylactoid or anaphylactic reactions attributable to treatment with canakinumab were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see section 4.3).

Hepatic function

Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

Vaccinations

No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks (see section 4.5).

Prior to initiation of canakinumab therapy it is recommended that adult and paediatric patients receive all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine (see section 4.5).

Mutation in NLRP3 gene in CAPS patients

Clinical experience in CAPS patients without a confirmed mutation in the NLRP3 gene is limited.

Macrophage activation syndrome in patients with Still's disease (SJIA and AOSD)

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still's disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. Based on clinical trial experience, canakinumab does not appear to increase the incidence of MAS in Still's disease patients, but no definitive conclusion can be made.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Ilaris, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, Ilaris should not be re-administered and a different treatment considered.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between canakinumab and other medicinal products have not been investigated in formal studies.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of canakinumab with TNF inhibitors is not recommended because this may increase the risk of serious infections.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of canakinumab treatment, the recommendation is to wait for at least 3 months after the last canakinumab injection and before the next one (see section 4.4).

The results of a study in healthy adult subjects demonstrated that a single dose of canakinumab 300 mg did not affect the induction and persistence of antibody responses after vaccination with influenza or glycosylated protein based meningococcus vaccines.

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women should use effective contraceptives during treatment with canakinumab and for up to 3 months after the last dose.

Pregnancy

There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the foetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of canakinumab before childbirth. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

Breast-feeding

It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during canakinumab therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility

Formal studies of the potential effect of canakinumab on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with canakinumab (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with canakinumab (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined 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 Tabulated list of adverse reactions

MedDRA System Organ Class	**Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis**
Infections and infestations	
Very common	Respiratory tract infections (including pneumonia, bronchitis, influenza, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection) Ear infection Cellulitis Gastroenteritis Urinary tract infection
Common	Vulvovaginal candidiasis
Nervous system disorders	
Common	Dizziness/vertigo
Gastrointestinal disorders	
Very common	Upper abdominal pain [1]
Uncommon	Gastro-oesophageal reflux disease [2]
Skin and subcutaneous tissue disorders	
Very common	Injection site reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia [1]
Common	Musculoskeletal pain [1] Back pain [2]
General disorders and administration site conditions	
Common	Fatigue/asthenia [2]
Investigations	
Very common	Creatinine renal clearance decreased [1,3] Proteinuria [1,4] Leukopenia [1,5]
Common	Neutropenia [5]
Uncommon	Platelet count decreased [5]

[1] In SJIA
[2] In gouty arthritis
[3] Based on estimated creatinine clearance, most were transient
[4] Most represented transient trace to 1+ positive urinary protein by dipstick
[5] See further information below

Still's Disease (SJIA and AOSD)

SJIA pooled analysis and AOSD

A total of 445 SJIA patients aged 2 to < 20 years received canakinumab in clinical trials, including 321 patients aged 2 to < 12 years, 88 patients aged 12 to < 16 years, and 36 patients aged 16 to < 20 years. A pooled safety analysis of all SJIA patients showed that in the subset of young adult SJIA patients aged 16 to < 20 years, the safety profile of canakinumab was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile of canakinumab in AOSD patients in a randomised, double blind placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients
During clinical trials with canakinumab in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with canakinumab without concomitant elevations of transaminases.

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, upper respiratory tract infection), vomiting and dizziness were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups.

Laboratory abnormalities in TRAPS, HIDS/MKD and FMF patients
Neutrophils
Although ≥ Grade 2 reductions in neutrophil count occurred in 6.5% of patients (common) and Grade 1 reductions occurred in 9.5% of patients, the reductions are generally transient and neutropenia-associated infection has not been identified as an adverse reaction.

Platelets
Although reductions in platelet count (≥ Grade 2) occurred in 0.6% of patients, bleeding has not been identified as an adverse reaction. Mild and transient Grade 1 reduction in platelets occurred in 15.9% of patients without any associated bleeding adverse events.

Laboratory abnormalities in SJIA patients
Haematology
In the overall SJIA programme, transient decreased white blood cell (WBC) counts ≤ 0.8 x LLN were reported in 33 patients (16.5%).

In the overall SJIA programme, transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/l were reported in 12 patients (6.0%).

In the overall SJIA programme, transient decreases in platelet counts (< LLN) were observed in 19 patients (9.5%).

ALT/AST
In the overall SJIA programme, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in 19 patients (9.5%).

Laboratory abnormalities in gouty arthritis patients
Haematology
Decreased white blood cell counts (WBC) ≤ 0.8 x lower limit of normal (LLN) were reported in 6.7% of patients treated with canakinumab compared to 1.4% treated with triamcinolone acetonide. Decreases in absolute neutrophil counts (ANC) to less than 1 x 10^9/l were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts < 0.5 x 10^9/l were also observed (see section 4.4).

Mild (< LLN and > 75 x 10^9/l) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with canakinumab in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid
Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after canakinumab treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST
Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the canakinumab-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with canakinumab-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides
In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in canakinumab-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with canakinumab and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Long term data from observational study

A total of 243 CAPS patients (85 paediatric patients aged ≥ 2 to ≤ 17 years and 158 adult patients aged ≥ 18 years) were treated with canakinumab in routine clinical practice in a long-term registry study (mean of 3.8 years of canakinumab exposure). The safety profile of canakinumab observed following long-term treatment in this setting was consistent with what has been observed in interventional studies in CAPS patients.

Paediatric population

There were 80 paediatric CAPS patients (2-17 years of age) who received canakinumab in the interventional studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of canakinumab appeared similar to that in patients aged 2 years and above.

There were 102 TRAPS, HIDS/MKD and FMF patients (2-17 years of age) who received canakinumab in a 16-week study. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall population.

Elderly population

There is no significant difference in safety profile observed in patients ≥ 65 years of age.

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

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

Pharmacodynamic effects

CAPS, TRAPS, HIDS/MKD and FMF
In clinical studies, CAPS, TRAPS, HIDS/MKD and FMF patients who have uncontrolled over-production of IL-1 beta show a rapid and sustained response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's disease (SJIA and AOSD)
Adult-onset Still's disease and systemic juvenile idiopathic arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of SJIA and AOSD include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see Clinical efficacy and safety).

Gouty arthritis
A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety

CAPS
The efficacy and safety of canakinumab have been demonstrated in a total of 211 adult and paediatric patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with canakinumab had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of canakinumab injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of canakinumab (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

- Part I: A complete clinical and biomarker response to canakinumab (defined as composite of physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values < 10 mg/litre) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms, and patient's assessment of symptoms.

- Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to canakinumab flared, compared with 81% of the patients randomised to placebo.

- Part III: Patients treated with placebo in Part II who flared regained and maintained clinical and serological response following entry into the open-label canakinumab extension.

Table 2 Tabulated summary of efficacy in Phase III trial, pivotal placebo-controlled withdrawal period (Part II)

Phase III trial, pivotal placebo-controlled withdrawal period (Part II)			
	Canakinumab N=15 n(%)	Placebo N=16 n(%)	p-value
Primary endpoint (flare)			
Proportion of patients with disease flare in Part II	0 (0%)	13 (81%)	< 0.001
Inflammatory markers*			
C-reactive protein, mg/l	1.10 (0.40)	19.93 (10.50)	< 0.001
Serum amyloid A, mg/l	2.27 (-0.20)	71.09 (14.35)	0.002
* mean (median) change from beginning of Part II			

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks, with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24, including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to < 4 years achieved complete response (57.1%) than older paediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every 8 weeks suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥ 15 kg and ≤ 40 kg). An increased dose was administered more frequently to patients aged 2 to < 4 years and to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

A 6-year observational registry study was conducted to provide data on the long-term safety and effectiveness of canakinumab treatment in paediatric and adult CAPS patients in routine clinical practice. The study included 243 CAPS patients (including 85 patients less than 18 years of age). Disease activity was rated as absent or mild/moderate in more than 90% of patients at all post-baseline time points in the study, and median serological markers of inflammation (CRP and SAA) were normal (< 10 mg/litre) at all post-baseline time points. Although approximately 22% of patients receiving canakinumab required dose adjustment, only a small percentage of patients (1.2%) discontinued canakinumab due to lack of therapeutic effect.

Paediatric population
The CAPS interventional trials with canakinumab included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of canakinumab in paediatric CAPS patients ≤ 4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

TRAPS, HIDS/MKD and FMF
The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were demonstrated in a single, pivotal, phase III, 4-part study (N2301) consisting of three separate disease cohorts.

- Part I: Patients in each disease cohort aged 2 years and older entered a 12-week screening period during which they were evaluated for the onset of disease flare.
- Part II: Patients at flare onset were randomised into a 16-week double-blind, placebo-controlled treatment period during which they received either 150 mg canakinumab (2 mg/kg for patients with body weight ≤ 40 kg) subcutaneous (s.c.) or placebo every 4 weeks. Patients > 28 days but < 2 years of age were allowed to enter the study directly into an open-arm of Part II as non-randomised patients (and were excluded from the primary efficacy analysis).
- Part III: Patients who completed 16 weeks of treatment and were classified as responders were re-randomised into a 24-week, double-blind withdrawal period during which they received canakinumab 150 mg (2 mg/kg for patients ≤ 40 kg) s.c. or placebo every 8 weeks.
- Part IV: All Part III patients treated with canakinumab were eligible to enter into a 72-week open-label treatment extension period.

A total of 185 patients aged 28 days and above were enrolled and a total of 181 patients aged 2 years and above were randomised in part II of the study.

The primary efficacy endpoint of the randomised treatment period (Part II) was the proportion of responders within each cohort who had resolution of their index disease flare at day 15 and did not experience a new flare during the remainder of the 16-week treatment period (defined as complete response). Resolution of the index disease flare was defined as having a Physician's Global Assessment (PGA) of Disease Activity score < 2 ("minimal or no disease") and CRP within normal range (≤ 10 mg/l) or reduction ≥ 70% from baseline. A new flare was defined as a PGA score ≥ 2 ("mild, moderate, or severe disease") and CRP ≥ 30 mg/l. Secondary endpoints, all based on week 16 results (end of Part II), included the proportion of patients who achieved a PGA score of < 2, the proportion of patients with serological remission (defined as CRP ≤ 10 mg/l), and the proportion of patients with a normalised SAA level (defined as SAA ≤ 10 mg/l).

For the primary efficacy endpoint, canakinumab was superior to placebo for all three disease cohorts. Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of PGA < 2 and CRP ≤ 10 mg/l in all three cohorts. Higher proportions of patients had normalised SAA (≤ 10 mg/l) at week 16 with canakinumab treatment compared to placebo in all three cohorts, with a statistically significant difference observed in TRAPS patients (see Table 3 with study results below).

Table 3 Tabulated summary of efficacy in Phase III trial, pivotal, randomised, placebo-controlled treatment period (Part II)

Phase III trial, pivotal, randomised placebo-controlled treatment period (Part II)			
	Canakinumab n/N (%)	Placebo n/N (%)	p-value
Primary endpoint (disease flare) - Proportion of patients who had index disease flare resolution at day 15 and did not experience a new flare during the remainder of the 16-week treatment period			
FMF	19/31 (61.29)	2/32 (6.25)	< 0.0001*
HIDS/MKD	13/37 (35.14)	2/35 (5.71)	0.0020*
TRAPS	10/22 (45.45)	2/24 (8.33)	0.0050*
Secondary endpoints (disease and inflammatory markers)			
Physician Global Assessment < 2			
FMF	20/31 (64.52)	3/32 (9.38)	< 0.0001**
HIDS/MKD	17/37 (45.95)	2/35 (5.71)	0.0006**
TRAPS	10/22 (45.45)	1/24 (4.17)	0.0028**
C-reactive protein ≤ 10 mg/l			
FMF	21/31 (67.74)	2/32 (6.25)	< 0.0001**
HIDS/MKD	15/37 (40.54)	2/35 (5.71)	0.0010**
TRAPS	8/22 (36.36)	2/24 (8.33)	0.0149**
Serum amyloid A ≤ 10 mg/l			
FMF	8/31 (25.81)	0/32 (0.00)	0.0286
HIDS/MKD	5/37 (13.51)	1/35 (2.86)	0.0778
TRAPS	6/22 (27.27)	0/24 (0.00)	0.0235**
n=number of responders; N=number of evaluable patients * indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test ** Indicates statistical significance (one-sided) at the 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA respectively, as explanatory variables for each cohort			

Up-titration
In Part II of the study, patients treated with canakinumab who had persistent disease activity received an additional dose of 150 mg (or 2 mg/kg for patients ≤ 40 kg) within the first month. This additional dose could be provided as early as 7 days after the first treatment dose. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients ≤ 40 kg) every 4 weeks.

In an exploratory analysis of the primary endpoint, it was observed that in patients with an inadequate response after the first dose, an up-titration within the first month to a dose of 300 mg (or 4 mg/kg) every 4 weeks further improved flare control, reduced disease activity and normalised CRP and SAA levels.

Paediatric patients:
Two non-randomised HIDS/MKD patients aged > 28 days but < 2 years were included in the study and received canakinumab. One patient had resolution of index flare by day 15 after receiving one single dose of canakinumab 2 mg/kg, but discontinued treatment after this first dose due to serious adverse events (pancytopenia and hepatic failure). This patient presented at study entry with a history of immune thrombocytopenic purpura and an active medical condition of abnormal hepatic function. The second patient received a starting dose of canakinumab 2 mg/kg and an add-on dose of 2 mg/kg at week 3, and was up-titrated at week 5 to receive a dose of 4 mg/kg administered every 4 weeks until the end of Part II of the study. Resolution of disease flare was achieved by week 5 and the patient had not experienced any new flare at the end of Part II of the study (week 16).

Still's disease (SJIA and AOSD)
SJIA
The efficacy of canakinumab for the treatment of active SJIA was assessed in two pivotal phase III studies (G2305 and G2301). Patients enrolled were aged 2 to < 20 years (mean age of 8.5 years and mean disease duration of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305
Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of canakinumab in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) canakinumab or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Canakinumab treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 4).

Table 4 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Canakinumab N=43	Placebo N=41	Canakinumab N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%
Treatment difference for all ACR scores was significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for canakinumab (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for canakinumab (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among canakinumab treated patients was consistent at day 29.

Study G2301
Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by canakinumab. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In Part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) canakinumab administered every 4 weeks for up to 32 weeks. Patients in Part II (double-blind) received either canakinumab 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:
Of the total 128 patients who entered Part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:
Patients taking canakinumab in Part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering Part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

Health-related and quality of life outcomes in studies G2305 and G2301
Treatment with canakinumab resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for canakinumab vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of Part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores were reported for canakinumab vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled efficacy analysis
Data from the first 12 weeks of canakinumab treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra may respond to canakinumab.

Study G2301E1
The efficacy observed in the studies G2305 and G2301 was maintained in the open-label long-term extension study G2301E1. Of the 270 SJIA patients in the study, 147 patients had received treatment with canakinumab in studies G2305 or G2301 (Cohort I), and 123 patients were canakinumab-naive patients (Cohort II). Patients in Cohort I were treated for a median duration of 3.2 years (up to 5.2 years), and patients in Cohort II were treated for a median duration of 1.8 years (up to 2.8 years). In the extension study, all patients received canakinumab 4 mg/kg (up to maximum 300 mg) every 4 weeks. In both cohorts, patients who were well-controlled responders (retrospectively defined as adapted paediatric ACR $\geq$ 90) and who did not require a concomitant corticosteroid were permitted to reduce their canakinumab dose to 2 mg/kg every 4 weeks (62/270; 23%).

Study G2306
Study G2306 was an open-label study to assess maintenance of treatment response with canakinumab dose reduction (2 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 8 weeks) in SJIA patients who were receiving canakinumab 4 mg/kg every 4 weeks. Seventy five patients aged 2 to 22 years who maintained inactive disease status for at least 6 consecutive months (clinical remission) with canakinumab monotherapy, including patients who were able to maintain inactive disease status with discontinuation of concomitant corticosteroid and/or methotrexate use for at least 4 weeks, were randomised to receive canakinumab 2 mg/kg every 4 weeks (N=38) or canakinumab 4 mg/kg every 8 weeks (N=37). After 24 weeks, 71% (27/38) of patients who received the reduced dose (2 mg/kg every 4 weeks) and 84% (31/37) of patients who received the prolonged dosing interval (4 mg/kg every 8 weeks) were able to maintain inactive disease status for 6 months. Of the patients in clinical remission who continued with further dose reduction (1 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 12 weeks), 93% (26/28) and 91% (30/33) of patients, respectively, were able to maintain inactive disease status for 6 months. Patients who maintained inactive disease status for 6 additional months at this lowest dose regimen were allowed to discontinue canakinumab. Overall, 33% (25/75) of patients randomised to dose reduction or dose interval prolongation arms were able to discontinue treatment with canakinumab and maintain inactive disease status for 6 months. The rate of adverse events in both treatment arms was similar to the rate seen in patients treated with canakinumab 4 mg/kg every 4 weeks.

AOSD
The efficacy of canakinumab 4 mg/kg (up to maximum 300 mg) administered every 4 weeks in AOSD patients in a randomised, double-blind placebo-controlled study in 36 patients (22 to 70 years old) was comparable to that observed in SJIA patients. In study GDE01T, a higher proportion of patients (12/18, 66.7%) in the canakinumab group than in the placebo group (7/17, 41.2%) demonstrated an improvement from baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28-ESR) of > 1.2 at week 12, which failed to reach statistical significance (odds ratio 2.86, treatment difference [%] 25.49 [95% CI: 9.43, 55.80]). By week 4, 7 of 18 patients (38.9%) treated with canakinumab had already achieved DAS28-ESR remission versus 2 of 17 patients (11.8%) on placebo. These data are consistent with the results of a pooled efficacy analysis of 418 SJIA patients which showed that the efficacy of canakinumab in a subset of SJIA patients aged 16 to < 20 years (n=34) was consistent with the efficacy observed in patients less than 16 years of age (n=384).

Gouty arthritis
The efficacy of canakinumab for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous canakinumab 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the canakinumab group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for canakinumab 150 mg compared with triamcinolone acetonide at 72 hours. Canakinumab also reduced the risk of subsequent attacks (see Table 5).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 5. Treatment with canakinumab induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 5 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	**Overall study population; N=454**	**Unable to use both NSAIDs and colchicine; on ULT N=62**
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337
* Denotes significant p-value ≤ 0.025		

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population
Overall, the efficacy, safety and tolerability profile of canakinumab in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)
In clinical studies, canakinumab has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity

Antibodies against canakinumab were observed in approximately 1.5%, 3% and 2% of the patients treated with canakinumab for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

There were no antibodies against canakinumab observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

Paediatric population

The Marketing Authorisation Holder has completed four Paediatric Investigation Plans for canakinumab (for CAPS, SJIA, FMF – HIDS/MKD and TRAPS respectively). This product information has been updated to include the results of studies with canakinumab in the paediatric population.

The European Medicines Agency has waived the obligation to submit the results of studies with canakinumab in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

Absorption
The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 µg/ml and 708 µg*d/ml. The absolute bioavailability of subcutaneously administered canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{,ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 µg/ml, 24.3 µg/ml, 767 µg*d/ml) compared to the weight categories < 40 kg (4.0 µg/ml, 19.9 µg/ml, 566 µg*d/ml) and > 70 kg (4.6 µg/ml, 17.8 µg/ml, 545 µg*d/ml). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution
Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination
The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA patients.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

TRAPS, HIDS/MKD and FMF

Bioavailability in TRAPS, HIDS/MKD and FMF patients has not been determined independently. Apparent clearance (CL/F) in the TRAPS, HIDS/MKD and FMF population at body weight of 55 kg (0.14 l/d) was comparable to CAPS population at body weight of 70 kg (0.17 l/d). The apparent volume of distribution (V/F) was 4.96 l at body weight of 55 kg.

After repeated subcutaneous administration of 150 mg every 4 weeks, canakinumab minimal concentration at week 16 (C_{min}) was estimated to be 15.4 ± 6.6 µg/ml. The estimated steady state AUC_{tau} was 636.7 ± 260.2 µg*d/ml.

Still's disease (SJIA and AOSD)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg. Sparse pharmacokinetics (PK) data in AOSD patients suggest similar PK of canakinumab as compared to SJIA and other patient populations.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (±SD) for $C_{min,ss}$, $C_{max,ss}$ and $AUC_{,ss4w}$ were 14.7±8.8 µg/ml, 36.5 ± 14.9 µg/ml and 696.1 ± 326.5 µg*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 µg*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{min,ss}$ (11.4 vs 19 µg/ml) and AUC_{ss} (594 vs 880 µg*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{max}: 10.8 µg/ml and AUC_{inf}: 495 µg*d/ml) was lower than in a typical 70 kg CAPS patient (15.9 µg/ml and 708 µg*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population

Peak concentrations of canakinumab occurred between 2 to 7 days (T_{max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric patients 4 years of age and older. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g. 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

In TRAPS, HIDS/MKD and FMF, exposure parameters (trough concentrations) were comparable across age groups from 2 to < 20 years old following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

Pharmacokinetic properties are similar in CAPS, TRAPS, HIDS/MKD, FMF and SJIA paediatric populations.

Elderly population

No change in pharmacokinetic parameters based on clearance or volume of distribution were observed between elderly patients and adult patients < 65 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cross-reactivity, repeated dose toxicity, immunotoxicity, toxicity to reproduction and development.

Formal carcinogenicity studies have not been conducted with canakinumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for injection in a vial (type I glass) with a stopper (coated chlorobutyl rubber) and flip-off cap (aluminium).

Packs containing 1 vial or multipacks containing 4 (4x1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use.

Instructions for reconstitution

Using aseptic technique, reconstitute each vial of canakinumab at room temperature (typically 15°C to 25°C) by slowly injecting 1 ml water for injections with a 1 ml syringe and an 18 G x 2 inch (50 mm) needle. Swirl the vial slowly at an angle of about 45° for approximately 1 minute and allow to stand for about 5 minutes. Then gently turn the vial upside down and back again ten times. If possible, avoid touching the rubber stopper with your fingers. Allow to stand for about 15 minutes at room temperature to obtain a clear to opalescent solution. Do not shake. Do not use if particles are present in the solution.

Tap the side of the vial to remove any residual liquid from the stopper. The solution should be free of visible particles and clear to opalescent. The solution should be colourless or may have a slight brownish-yellow tint. If the solution has a distinctly brown discolouration it should not be used. If not used immediately after reconstitution, the solution should be kept at 2°C to 8°C and used within 24 hours.

Instructions for administration

Carefully withdraw the required volume depending on the dose to be administered (0.1 ml to 1 ml) and subcutaneously inject using a 27 G x 0.5 inch (13 mm) needle.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009
Date of latest renewal: 06 June 2019

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 mg of canakinumab*.

Each ml of solution contains 150 mg canakinumab.

* human monoclonal antibody produced in mouse myeloma Sp2/0 cells by 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 opalescent and colourless to slightly brownish yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Periodic fever syndromes

Ilaris is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents and children aged 2 years and older:

Cryopyrin-associated periodic syndromes
Ilaris is indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including:

- Muckle-Wells syndrome (MWS),
- Neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular syndrome (CINCA),
- Severe forms of familial cold autoinflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS)
Ilaris is indicated for the treatment of tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS).

Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)
Ilaris is indicated for the treatment of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Familial Mediterranean fever (FMF)
Ilaris is indicated for the treatment of Familial Mediterranean Fever (FMF). Ilaris should be given in combination with colchicine, if appropriate.

Ilaris is also indicated for the treatment of:

Still's disease

Ilaris is indicated for the treatment of active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

Gouty arthritis

Ilaris is indicated for the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate (see section 5.1).

4.2 Posology and method of administration

For CAPS, TRAPS, HIDS/MKD, FMF and Still's disease, the treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.

For gouty arthritis, the physician should be experienced in the use of biologics and Ilaris should be administered by a healthcare professional.

Posology

CAPS: Adults, adolescents and children aged 2 years and older
The recommended starting dose of canakinumab for CAPS patients is:
Adults, adolescents and children ≥ 4 years of age:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg
- 4 mg/kg for patients with body weight ≥ 7.5 kg and < 15 kg

Children 2 to < 4 years of age:

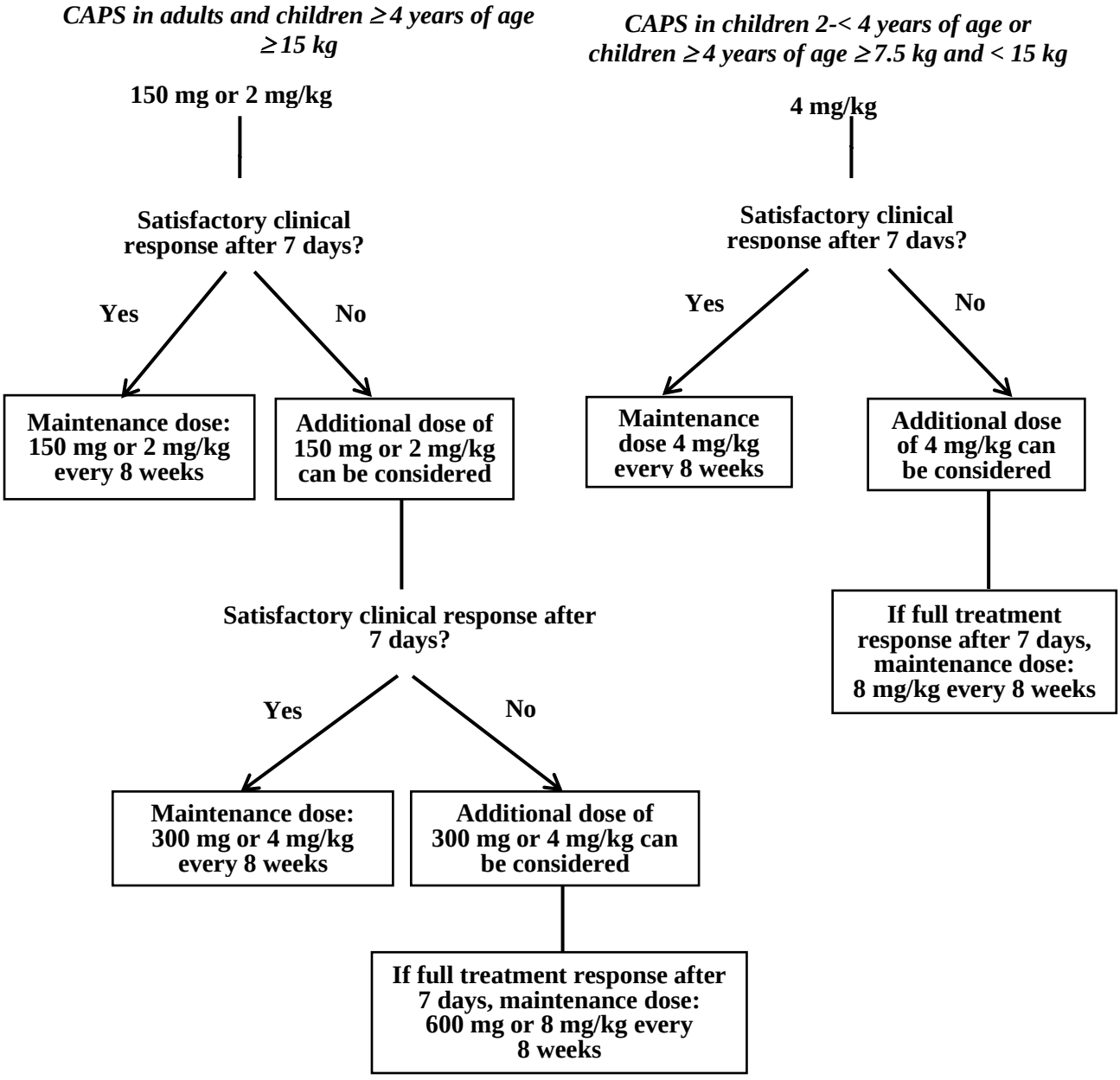
- 4 mg/kg for patients with body weight ≥ 7.5 kg

This is administered every eight weeks as a single dose via subcutaneous injection.

For patients with a starting dose of 150 mg or 2 mg/kg, if a satisfactory clinical response (resolution of rash and other generalised inflammatory symptoms) has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg or 4 mg/kg every 8 weeks should be maintained. If a satisfactory clinical response has not been achieved 7 days after this increased dose, a third dose of canakinumab at 300 mg or 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 600 mg or 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

For patients with a starting dose of 4 mg/kg, if a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab 4 mg/kg can be considered. If a full treatment response is subsequently achieved, maintaining the intensified dosing regimen of 8 mg/kg every 8 weeks should be considered, based on individual clinical judgement.

Clinical experience with dosing at intervals of less than 4 weeks or at doses above 600 mg or 8 mg/kg is limited.



TRAPS, HIDS/MKD and FMF: Adults, adolescents and children aged 2 years and older

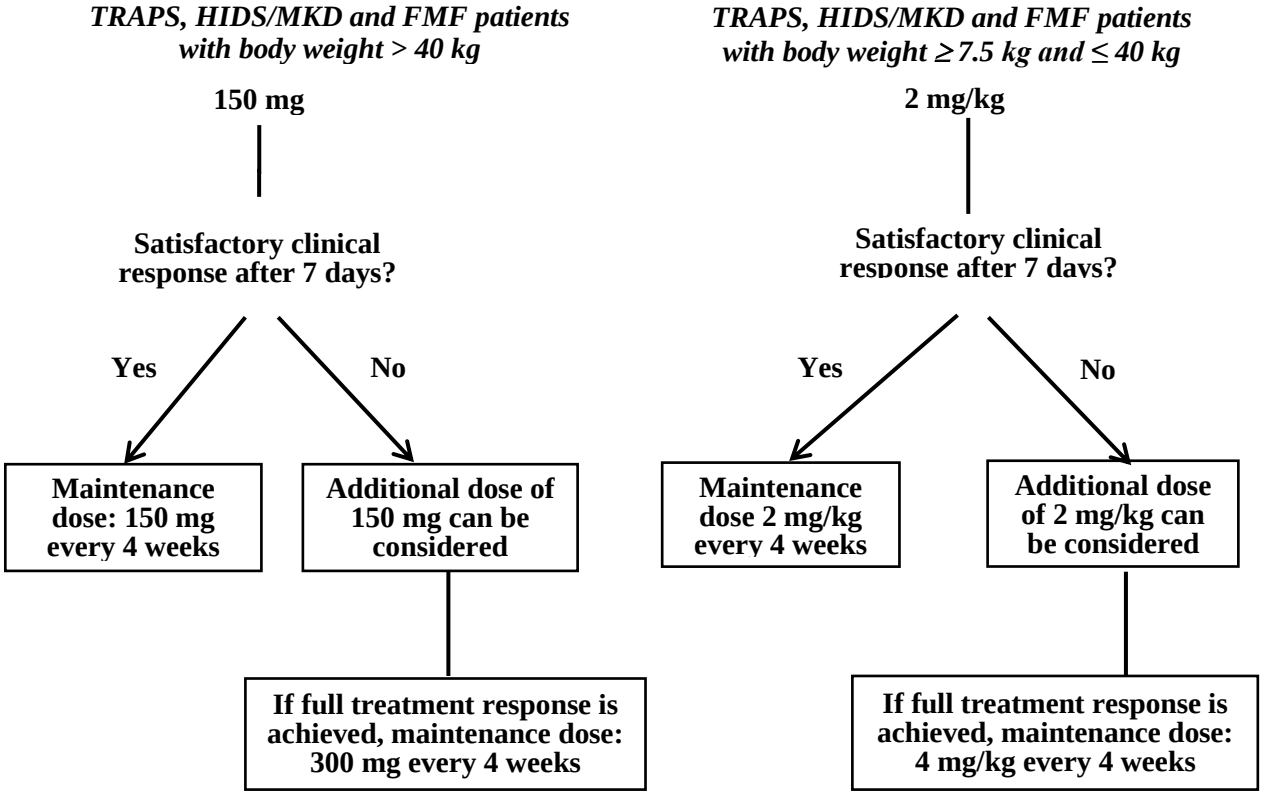
The recommended starting dose of canakinumab in TRAPS, HIDS/MKD and FMF patients is:

- 150 mg for patients with body weight > 40 kg
- 2 mg/kg for patients with body weight ≥ 7.5 kg and ≤ 40 kg

This is administered every four weeks as a single dose via subcutaneous injection.

If a satisfactory clinical response has not been achieved 7 days after treatment start, a second dose of canakinumab at 150 mg or 2 mg/kg can be considered. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) every 4 weeks should be maintained.

Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.



Still's disease (SJIA and AOSD)
The recommended dose of canakinumab for patients with Still's disease with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every four weeks via subcutaneous injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician.

Gouty arthritis
Management of hyperuricaemia with appropriate urate lowering therapy (ULT) should be instituted or optimised. Canakinumab should be used as an on-demand therapy to treat gouty arthritis attacks.

The recommended dose of canakinumab for adult patients with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack.

Patients who do not respond to initial treatment should not be re-treated with canakinumab. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered (see section 5.2).

Special populations

Paediatric population
CAPS, TRAPS, HIDS/MKD and FMF
The safety and efficacy of canakinumab in CAPS, *TRAPS, HIDS/MKD and FMF* patients under 2 years of age have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

SJIA
The safety and efficacy of canakinumab in SJIA patients under 2 years of age have not been established. No data are available.

Gouty arthritis
There is no relevant use of canakinumab in the paediatric population in the indication gouty arthritis.

Elderly
No dose adjustment is required.

Hepatic impairment
Canakinumab has not been studied in patients with hepatic impairment. No recommendation on a posology can be made.

Renal impairment
No dose adjustment is needed in patients with renal impairment. However, clinical experience in such patients is limited.

Method of administration

For subcutaneous use.
The following are suitable injection sites: upper thigh, abdomen, upper arm or buttocks. It is recommended to select a different injection site each time the product is injected to avoid soreness. Broken skin and areas which are bruised or covered by a rash should be avoided. Injection into scar tissue should be avoided as this may result in insufficient exposure to canakinumab.

Each vial is for single use in a single patient, for a single dose.

After proper training in the correct injection technique, patients or their caregivers may inject canakinumab if the physician determines that it is appropriate and with medical follow-up as necessary (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Canakinumab is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with canakinumab. Physicians should exercise caution when administering canakinumab to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.

Treatment of CAPS, TRAPS, HIDS/MKD, FMF and Still's disease (SJIA and AOSD)
Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention.

Treatment of gouty arthritis
Canakinumab should not be administered during an active infection.
Concomitant use of canakinumab with tumour necrosis factor (TNF) inhibitors is not recommended because this may increase the risk of serious infections (see section 4.5).

Isolated cases of unusual or opportunistic infections (including aspergillosis, atypical mycobacterial infections, herpes zoster) have been reported during canakinumab treatment. The causal relationship of canakinumab to these events cannot be excluded.

Tuberculosis screening

In approximately 12% of CAPS patients tested with a PPD (purified protein derivative) skin test in clinical trials, follow-up testing yielded a positive test result while treated with canakinumab without clinical evidence of a latent or active tuberculosis infection.

It is unknown whether the use of interleukin-1 (IL-1) inhibitors such as canakinumab increases the risk of reactivation of tuberculosis. Before initiation of therapy, all patients must be evaluated for both active and latent tuberculosis infection. Particularly in adult patients, this evaluation should include a detailed medical history. Appropriate screening tests (e.g. tuberculin skin test, interferon gamma release assay or chest X-ray) should be performed in all patients (local recommendations may apply). Patients must be monitored closely for signs and symptoms of tuberculosis during and after treatment with canakinumab. All patients should be instructed to seek medical advice if signs or symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, subfebrile temperature) appear during canakinumab therapy. In the event of conversion from a negative to a positive PPD test, especially in high-risk patients, alternative means of screening for a tuberculosis infection should be considered.

Neutropenia and leukopenia

Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including canakinumab. Treatment with canakinumab should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies

Malignancy events have been reported in patients treated with canakinumab. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions

Hypersensitivity reactions with canakinumab therapy have been reported. The majority of these events were mild in severity. During clinical development of canakinumab in over 2,600 patients, no anaphylactoid or anaphylactic reactions attributable to treatment with canakinumab were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded (see section 4.3).

Hepatic function

Transient and asymptomatic cases of elevations of serum transaminases or bilirubin have been reported in clinical trials (see section 4.8).

Vaccinations

No data are available on the risk of secondary transmission of infection by live (attenuated) vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks (see section 4.5).

Prior to initiation of canakinumab therapy it is recommended that adult and paediatric patients receive all vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine (see section 4.5).

Mutation in NLRP3 gene in CAPS patients

Clinical experience in CAPS patients without a confirmed mutation in the NLRP3 gene is limited.

Macrophage activation syndrome in patients with Still’s disease (SJIA and AOSD)

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular Still’s disease. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still’s disease, as these are known triggers for MAS. Based on clinical trial experience, canakinumab does not appear to increase the incidence of MAS in Still’s disease patients, but no definitive conclusion can be made.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Ilaris, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, Ilaris should not be re-administered and a different treatment considered.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between canakinumab and other medicinal products have not been investigated in formal studies.

An increased incidence of serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Use of canakinumab with TNF inhibitors is not recommended because this may increase the risk of serious infections.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as interleukin-1 beta (IL-1 beta). Thus, CYP450 expression may be reversed when potent cytokine inhibitory therapy, such as canakinumab, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of canakinumab in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently with canakinumab unless the benefits clearly outweigh the risks. Should vaccination with live vaccines be indicated after initiation of canakinumab treatment, the recommendation is to wait for at least 3 months after the last canakinumab injection and before the next one (see section 4.4).

The results of a study in healthy adult subjects demonstrated that a single dose of canakinumab 300 mg did not affect the induction and persistence of antibody responses after vaccination with influenza or glycosylated protein based meningococcus vaccines.

The results of a 56-week, open label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective antibody levels.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women should use effective contraceptives during treatment with canakinumab and for up to 3 months after the last dose.

Pregnancy

There is a limited amount of data from the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The risk for the foetus/mother is unknown. Women who are pregnant or who desire to become pregnant should therefore only be treated after a thorough benefit-risk evaluation.

Animal studies indicate that canakinumab crosses the placenta and is detectable in the foetus. No human data are available, but as canakinumab is an immunoglobulin of the G class (IgG1), human transplacental transfer is expected. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of canakinumab before childbirth. Women who received canakinumab during pregnancy should be instructed to inform the baby's healthcare professional before any vaccinations are given to their newborn infant.

Breast-feeding

It is unknown whether canakinumab is excreted in human milk. The decision whether to breast-feed during canakinumab therapy should therefore only be taken after a thorough benefit-risk evaluation.

Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups and that the antibody was transferred to them (see section 5.3).

Fertility

Formal studies of the potential effect of canakinumab on human fertility have not been conducted. Canakinumab had no effect on male fertility parameters in marmosets (*C. jacchus*). A murine anti-murine IL-1 beta antibody had no undesirable effects on fertility in male or female mice (see section 5.3).

4.7 Effects on ability to drive and use machines

Ilaris has minor influence on the ability to drive and use machines. Treatment with Ilaris may result in dizziness/vertigo or asthenia (see section 4.8). Patients who experience such symptoms during Ilaris treatment should wait for this to resolve completely before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions were infections predominantly of the upper respiratory tract. No impact on the type or frequency of adverse drug reactions was seen with longer-term treatment.

Hypersensitivity reactions have been reported in patients treated with canakinumab (see sections 4.3 and 4.4).

Opportunistic infections have been reported in patients treated with canakinumab (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency category with the most common first. Frequency categories are defined 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 Tabulated list of adverse reactions

MedDRA System Organ Class	**Indications: CAPS, TRAPS, HIDS/MKD, FMF, SJIA, gouty arthritis**
Infections and infestations	
Very common	Respiratory tract infections (including pneumonia, bronchitis, influenza, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection) Ear infection Cellulitis Gastroenteritis Urinary tract infection
Common	Vulvovaginal candidiasis
Nervous system disorders	
Common	Dizziness/vertigo
Gastrointestinal disorders	
Very common	Upper abdominal pain [1]
Uncommon	Gastro-oesophageal reflux disease [2]
Skin and subcutaneous tissue disorders	
Very common	Injection site reaction
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia [1]
Common	Musculoskeletal pain [1] Back pain [2]
General disorders and administration site conditions	
Common	Fatigue/asthenia [2]
Investigations	
Very common	Creatinine renal clearance decreased [1,3] Proteinuria [1,4] Leukopenia [1,5]
Common	Neutropenia [5]
Uncommon	Platelet count decreased [5]

[1] In SJIA
[2] In gouty arthritis
[3] Based on estimated creatinine clearance, most were transient
[4] Most represented transient trace to 1+ positive urinary protein by dipstick
[5] See further information below

Still's Disease (SJIA and AOSD)

SJIA pooled analysis and AOSD

A total of 445 SJIA patients aged 2 to < 20 years received canakinumab in clinical trials, including 321 patients aged 2 to < 12 years, 88 patients aged 12 to < 16 years, and 36 patients aged 16 to < 20 years. A pooled safety analysis of all SJIA patients showed that in the subset of young adult SJIA patients aged 16 to < 20 years, the safety profile of canakinumab was consistent with what was observed in SJIA patients less than 16 years of age. The safety profile of canakinumab in AOSD patients in a randomised, double blind placebo-controlled study (GDE01T) in 36 adult patients (aged 22 to 70 years) was similar to what was observed in SJIA patients.

Description of selected adverse reactions

Long-term data and laboratory abnormalities in CAPS patients
During clinical trials with canakinumab in CAPS patients mean values for haemoglobin increased and those for white blood cell, neutrophils and platelets decreased.

Elevations of transaminases have been observed rarely in CAPS patients.

Asymptomatic and mild elevations of serum bilirubin have been observed in CAPS patients treated with canakinumab without concomitant elevations of transaminases.

In the long-term, open-label studies with dose escalation, events of infections (gastroenteritis, respiratory tract infection, upper respiratory tract infection), vomiting and dizziness were more frequently reported in the 600 mg or 8 mg/kg dose group than in other dose groups.

Laboratory abnormalities in TRAPS, HIDS/MKD and FMF patients
Neutrophils
Although ≥ Grade 2 reductions in neutrophil count occurred in 6.5% of patients (common) and Grade 1 reductions occurred in 9.5% of patients, the reductions are generally transient and neutropenia-associated infection has not been identified as an adverse reaction.

Platelets
Although reductions in platelet count (≥ Grade 2) occurred in 0.6% of patients, bleeding has not been identified as an adverse reaction. Mild and transient Grade 1 reduction in platelets occurred in 15.9% of patients without any associated bleeding adverse events.

Laboratory abnormalities in SJIA patients
Haematology
In the overall SJIA programme, transient decreased white blood cell (WBC) counts ≤ 0.8 x LLN were reported in 33 patients (16.5%).

In the overall SJIA programme, transient decreases in absolute neutrophil count (ANC) to less than 1 x 10^9/l were reported in 12 patients (6.0%).

In the overall SJIA programme, transient decreases in platelet counts (< LLN) were observed in 19 patients (9.5%).

ALT/AST
In the overall SJIA programme, high ALT and/or AST > 3 x upper limit of normal (ULN) were reported in 19 patients (9.5%).

Laboratory abnormalities in gouty arthritis patients
Haematology
Decreased white blood cell counts (WBC) ≤ 0.8 x lower limit of normal (LLN) were reported in 6.7% of patients treated with canakinumab compared to 1.4% treated with triamcinolone acetonide. Decreases in absolute neutrophil counts (ANC) to less than 1 x 10^9/l were reported in 2% of patients in the comparative trials. Isolated cases of ANC counts < 0.5 x 10^9/l were also observed (see section 4.4).

Mild (< LLN and > 75 x 10^9/l) and transient decreases in platelet counts were observed at a higher incidence (12.7%) with canakinumab in the active-controlled clinical studies versus the comparator (7.7%) in gouty arthritis patients.

Uric acid
Increases in uric acid level (0.7 mg/dl at 12 weeks and 0.5 mg/dl at 24 weeks) were observed after canakinumab treatment in comparative trials in gouty arthritis. In another study, among patients who were starting on ULT, increases in uric acid were not observed. Uric acid increases were not observed in clinical trials in non-gouty arthritis populations (see section 5.1).

ALT/AST
Mean and median increases in alanine transaminase (ALT) of 3.0 U/l and 2.0 U/l, respectively, and in aspartate transaminase (AST) of 2.7 U/l and 2.0 U/l, respectively, from baseline to end of study were seen in the canakinumab-treated groups versus the triamcinolone acetonide-treated group(s), however the incidence of clinically significant changes (≥ 3 x the upper limit of normal) was greater for patients treated with triamcinolone acetonide (2.5% for both AST and ALT) compared with canakinumab-treated patients (1.6% for ALT and 0.8% for AST).

Triglycerides
In active-controlled gouty arthritis trials, there was a mean increase in triglycerides of 33.5 mg/dl in canakinumab-treated patients compared with a modest decrease of -3.1 mg/dl with triamcinolone acetonide. The incidence of patients with triglyceride elevations > 5 x upper limit of normal (ULN) was 2.4% with canakinumab and 0.7% with triamcinolone acetonide. The clinical significance of this observation is unknown.

Long term data from observational study

A total of 243 CAPS patients (85 paediatric patients aged ≥ 2 to ≤ 17 years and 158 adult patients aged ≥ 18 years) were treated with canakinumab in routine clinical practice in a long-term registry study (mean of 3.8 years of canakinumab exposure). The safety profile of canakinumab observed following long-term treatment in this setting was consistent with what has been observed in interventional studies in CAPS patients.

Paediatric population

There were 80 paediatric CAPS patients (2-17 years of age) who received canakinumab in the interventional studies. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population (comprised of adult and paediatric patients, N=211), including the overall frequency and severity of infectious episodes. Infections of the upper respiratory tract were the most frequently reported infection events.

Additionally, 6 paediatric patients under the age of 2 years were evaluated in a small open-label clinical study. The safety profile of canakinumab appeared similar to that in patients aged 2 years and above.

There were 102 TRAPS, HIDS/MKD and FMF patients (2-17 years of age) who received canakinumab in a 16-week study. Overall, there were no clinically meaningful differences in the safety and tolerability profile of canakinumab in paediatric patients compared to the overall population.

Elderly population

There is no significant difference in safety profile observed in patients ≥ 65 years of age.

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

Reported experience with overdose is limited. In early clinical trials, patients and healthy volunteers received doses as high as 10 mg/kg, administered intravenously or subcutaneously, without evidence of acute toxicity.

In case of overdose, it is recommended for the patient to be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC08

Mechanism of action

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.

Pharmacodynamic effects

CAPS, TRAPS, HIDS/MKD and FMF
In clinical studies, CAPS, TRAPS, HIDS/MKD and FMF patients who have uncontrolled over-production of IL-1 beta show a rapid and sustained response to therapy with canakinumab, i.e. laboratory parameters such as high C-reactive protein (CRP) and serum amyloid A (SAA), high neutrophil and platelet counts, and leukocytosis rapidly returned to normal.

Still's disease (SJIA and AOSD)
Adult-onset Still's disease and systemic juvenile idiopathic arthritis are severe autoinflammatory diseases, driven by innate immunity by means of pro-inflammatory cytokines, a key one being IL-1-beta.

Common features of SJIA and AOSD include fever, rash, hepatosplenomegaly, lymphadenopathy, polyserositis and arthritis. Treatment with canakinumab resulted in a rapid and sustained improvement of both the articular and the systemic features of SJIA with significant reduction of the number of inflamed joints, prompt resolution of fever and reduction of acute phase reactants in the majority of patients (see Clinical efficacy and safety).

Gouty arthritis
A gouty arthritis attack is caused by urate (monosodium urate monohydrate) crystals in the joint and surrounding tissue, which trigger resident macrophages to produce IL-1 beta via the "NALP3 inflammasome" complex. Activation of macrophages and concomitant over-production of IL-1 beta results in an acute painful inflammatory response. Other activators of the innate immune system, such as endogenous agonists of toll-like receptors, may contribute to the transcriptional activation of the IL-1 beta gene, initiating a gouty arthritis attack. Following canakinumab treatment, the inflammatory markers CRP or SAA and signs of acute inflammation (e.g. pain, swelling, redness) in the affected joint subside rapidly.

Clinical efficacy and safety

CAPS
The efficacy and safety of canakinumab have been demonstrated in a total of 211 adult and paediatric patients with varying degrees of disease severity and different CAPS phenotypes (including FCAS/FCU, MWS, and NOMID/CINCA). Only patients with confirmed NLRP3 mutation were included in the pivotal study.

In the Phase I/II study, treatment with canakinumab had a rapid onset of action, with disappearance or clinically significant improvement of symptoms within one day after dosing. Laboratory parameters such as high CRP and SAA, high neutrophils and platelet counts normalised rapidly within days of canakinumab injection.

The pivotal study consisted of a 48-week three-part multicentre study, i.e. an 8-week open-label period (Part I), a 24-week randomised, double-blind, placebo-controlled withdrawal period (Part II), followed by a 16-week open-label period (Part III). The aim of the study was to assess efficacy, safety, and tolerability of canakinumab (150 mg or 2 mg/kg every 8 weeks) in patients with CAPS.

– Part I: A complete clinical and biomarker response to canakinumab (defined as composite of physician's global assessment on autoinflammatory and on skin disease ≤ minimal and CRP or SAA values < 10 mg/litre) was observed in 97% of patients and appeared within 7 days of initiation of treatment. Significant improvements were seen in physician's clinical assessment of autoinflammatory disease activity: global assessment of autoinflammatory disease activity, assessment of skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, assessment of other related symptoms, and patient's assessment of symptoms.

– Part II: In the withdrawal period of the pivotal study, the primary endpoint was defined as the proportion of patients with a disease relapse/flare: none (0%) of the patients randomised to canakinumab flared, compared with 81% of the patients randomised to placebo.

– Part III: Patients treated with placebo in Part II who flared regained and maintained clinical and serological response following entry into the open-label canakinumab extension.

Table 2 Tabulated summary of efficacy in Phase III trial, pivotal placebo-controlled withdrawal period (Part II)

Phase III trial, pivotal placebo-controlled withdrawal period (Part II)			
	Canakinumab N=15 n(%)	Placebo N=16 n(%)	p-value
Primary endpoint (flare)			
Proportion of patients with disease flare in Part II	0 (0%)	13 (81%)	< 0.001
Inflammatory markers*			
C-reactive protein, mg/l	1.10 (0.40)	19.93 (10.50)	< 0.001
Serum amyloid A, mg/l	2.27 (-0.20)	71.09 (14.35)	0.002
* mean (median) change from beginning of Part II			

Two open-label, uncontrolled, long-term phase III studies were performed. One was a safety, tolerability, and efficacy study of canakinumab in patients with CAPS. The total treatment duration ranged from 6 months to 2 years. The other was an open-label study with canakinumab to evaluate the efficacy and safety in Japanese CAPS patients for 24 weeks, with an extension phase up to 48 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24, including those patients whose dose was increased.

In the pooled efficacy analysis for these two studies, 65.6% of patients who had not previously been treated with canakinumab achieved complete response at 150 mg or 2 mg/kg, while 85.2% of patients achieved complete response at any dose. Of the patients treated with 600 mg or 8 mg/kg (or even higher), 43.8% achieved complete response. Fewer patients aged 2 to < 4 years achieved complete response (57.1%) than older paediatric and adult patients. Of the patients who had achieved a complete response, 89.3% maintained response without relapsing.

Experience from individual patients who achieved a complete response following dose escalation to 600 mg (8 mg/kg) every 8 weeks suggests that a higher dose may be beneficial in patients not achieving complete response or not maintaining complete response with the recommended doses (150 mg or 2 mg/kg for patients ≥ 15 kg and ≤ 40 kg). An increased dose was administered more frequently to patients aged 2 to < 4 years and to patients with NOMID/CINCA symptoms compared with FCAS or MWS.

A 6-year observational registry study was conducted to provide data on the long-term safety and effectiveness of canakinumab treatment in paediatric and adult CAPS patients in routine clinical practice. The study included 243 CAPS patients (including 85 patients less than 18 years of age). Disease activity was rated as absent or mild/moderate in more than 90% of patients at all post-baseline time points in the study, and median serological markers of inflammation (CRP and SAA) were normal (< 10 mg/litre) at all post-baseline time points. Although approximately 22% of patients receiving canakinumab required dose adjustment, only a small percentage of patients (1.2%) discontinued canakinumab due to lack of therapeutic effect.

Paediatric population
The CAPS interventional trials with canakinumab included a total of 80 paediatric patients with an age range from 2 to 17 years (approximately half of them treated on an mg/kg basis). Overall, there were no clinically meaningful differences in the efficacy, safety and tolerability profile of canakinumab in paediatric patients compared to the overall CAPS population. The majority of paediatric patients achieved improvement in clinical symptoms and objective markers of inflammation (e.g. SAA and CRP).

A 56-week, open-label study was conducted to assess the efficacy, safety and tolerability of canakinumab in paediatric CAPS patients ≤ 4 years of age. Seventeen patients (including 6 patients under the age of 2 years) were evaluated, using weight-based starting doses of 2-8 mg/kg. The study also evaluated the effect of canakinumab on the development of antibodies to standard childhood vaccines. No differences in safety or efficacy were observed in patients under the age of 2 years compared with patients aged 2 years and above. All patients who received non-live, standard of care childhood vaccinations (N=7) developed protective antibody levels.

TRAPS, HIDS/MKD and FMF
The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD and FMF were demonstrated in a single, pivotal, phase III, 4-part study (N2301) consisting of three separate disease cohorts.

- Part I: Patients in each disease cohort aged 2 years and older entered a 12-week screening period during which they were evaluated for the onset of disease flare.
- Part II: Patients at flare onset were randomised into a 16-week double-blind, placebo-controlled treatment period during which they received either 150 mg canakinumab (2 mg/kg for patients with body weight ≤ 40 kg) subcutaneous (s.c.) or placebo every 4 weeks. Patients > 28 days but < 2 years of age were allowed to enter the study directly into an open-arm of Part II as non-randomised patients (and were excluded from the primary efficacy analysis).
- Part III: Patients who completed 16 weeks of treatment and were classified as responders were re-randomised into a 24-week, double-blind withdrawal period during which they received canakinumab 150 mg (2 mg/kg for patients ≤ 40 kg) s.c. or placebo every 8 weeks.
- Part IV: All Part III patients treated with canakinumab were eligible to enter into a 72-week open-label treatment extension period.

A total of 185 patients aged 28 days and above were enrolled and a total of 181 patients aged 2 years and above were randomised in part II of the study.

The primary efficacy endpoint of the randomised treatment period (Part II) was the proportion of responders within each cohort who had resolution of their index disease flare at Day 15 and did not experience a new flare during the remainder of the 16-week treatment period (defined as complete response). Resolution of the index disease flare was defined as having a Physician's Global Assessment (PGA) of Disease Activity score < 2 ("minimal or no disease") and CRP within normal range (≤ 10 mg/l) or reduction ≥ 70% from baseline. A new flare was defined as a PGA score ≥ 2 ("mild, moderate, or severe disease") and CRP ≥ 30 mg/l. Secondary endpoints, all based on week 16 results (end of Part II), included the proportion of patients who achieved a PGA score of < 2, the proportion of patients with serological remission (defined as CRP ≤ 10 mg/l), and the proportion of patients with a normalised SAA level (defined as SAA ≤ 10 mg/l).

For the primary efficacy endpoint, canakinumab was superior to placebo for all three disease cohorts. Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of PGA < 2 and CRP ≤ 10 mg/l in all three cohorts. Higher proportions of patients had normalised SAA (≤ 10 mg/l) at week 16 with canakinumab treatment compared to placebo in all three cohorts, with a statistically significant difference observed in TRAPS patients (see Table 3 with study results below).

Table 3 Tabulated summary of efficacy in Phase III trial, pivotal, randomised, placebo-controlled treatment period (Part II)

Phase III trial, pivotal, randomised placebo-controlled treatment period (Part II)			
	Canakinumab n/N (%)	Placebo n/N (%)	p-value
Primary endpoint (disease flare) - Proportion of patients who had index disease flare resolution at day 15 and did not experience a new flare during the remainder of the 16-week treatment period			
FMF	19/31 (61.29)	2/32 (6.25)	< 0.0001*
HIDS/MKD	13/37 (35.14)	2/35 (5.71)	0.0020*
TRAPS	10/22 (45.45)	2/24 (8.33)	0.0050*
Secondary endpoints (disease and inflammatory markers)			
Physician Global Assessment < 2			
FMF	20/31 (64.52)	3/32 (9.38)	< 0.0001**
HIDS/MKD	17/37 (45.95)	2/35 (5.71)	0.0006**
TRAPS	10/22 (45.45)	1/24 (4.17)	0.0028**
C-reactive protein ≤ 10 mg/l			
FMF	21/31 (67.74)	2/32 (6.25)	< 0.0001**
HIDS/MKD	15/37 (40.54)	2/35 (5.71)	0.0010**
TRAPS	8/22 (36.36)	2/24 (8.33)	0.0149**
Serum amyloid A ≤ 10 mg/l			
FMF	8/31 (25.81)	0/32 (0.00)	0.0286
HIDS/MKD	5/37 (13.51)	1/35 (2.86)	0.0778
TRAPS	6/22 (27.27)	0/24 (0.00)	0.0235**
n=number of responders; N=number of evaluable patients * indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test **Indicates statistical significance (one-sided) at the 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP or SAA respectively, as explanatory variables for each cohort			

Up-titration
In Part II of the study, patients treated with canakinumab who had persistent disease activity received an additional dose of 150 mg (or 2 mg/kg for patients ≤ 40 kg) within the first month. This additional dose could be provided as early as 7 days after the first treatment dose. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients ≤ 40 kg) every 4 weeks.

In an exploratory analysis of the primary endpoint, it was observed that in patients with an inadequate response after the first dose, an up-titration within the first month to a dose of 300 mg (or 4 mg/kg) every 4 weeks further improved flare control, reduced disease activity and normalised CRP and SAA levels.

Paediatric patients:
Two non-randomised HIDS/MKD patients aged > 28 days but < 2 years were included in the study and received canakinumab. One patient had resolution of index flare by day 15 after receiving one single dose of canakinumab 2 mg/kg, but discontinued treatment after this first dose due to serious adverse events (pancytopenia and hepatic failure). This patient presented at study entry with a history of immune thrombocytopenic purpura and an active medical condition of abnormal hepatic function. The second patient received a starting dose of canakinumab 2 mg/kg and an add-on dose of 2 mg/kg at week 3, and was up-titrated at week 5 to receive a dose of 4 mg/kg administered every 4 weeks until the end of Part II of the study. Resolution of disease flare was achieved by week 5 and the patient had not experienced any new flare at the end of Part II of the study (week 16).

Still's disease (SJIA and AOSD)
SJIA
The efficacy of canakinumab for the treatment of active SJIA was assessed in two pivotal phase III studies (G2305 and G2301). Patients enrolled were aged 2 to < 20 years (mean age of 8.5 years and mean disease duration of 3.5 years at baseline) and had active disease defined as ≥ 2 joints with active arthritis, fever and elevated CRP.

Study G2305
Study G2305 was a randomised, double-blind, placebo-controlled, 4-week study assessing the short-term efficacy of canakinumab in 84 patients randomised to receive a single dose of 4 mg/kg (up to 300 mg) canakinumab or placebo. The primary objective was the proportion of patients at day 15 who achieved a minimum 30% improvement in the paediatric American College of Rheumatology (ACR) response criterion adapted to include absence of fever. Canakinumab treatment improved all paediatric ACR response scores as compared to placebo at days 15 and 29 (Table 4).

Table 4 Paediatric ACR response and disease status at days 15 and 29

	Day 15		Day 29	
	Canakinumab N=43	Placebo N=41	Canakinumab N=43	Placebo N=41
ACR30	84%	10%	81%	10%
ACR50	67%	5%	79%	5%
ACR70	61%	2%	67%	2%
ACR90	42%	0%	47%	2%
ACR100	33%	0%	33%	2%
Inactive disease	33%	0%	30%	0%
Treatment difference for all ACR scores was significant ($p \leq 0.0001$)				

Results for the components of the adapted paediatric ACR which included systemic and arthritic components, were consistent with the overall ACR response results. At day 15, the median change from baseline in the number of joints with active arthritis and limited range of motion were -67% and -73% for canakinumab (N=43), respectively, compared to a median change of 0% and 0% for placebo (N=41). The mean change in patient pain score (0-100 mm visual analogue scale) at day 15 was -50.0 mm for canakinumab (N=43), as compared to +4.5 mm for placebo (N=25). The mean change in pain score among canakinumab treated patients was consistent at day 29.

Study G2301
Study G2301 was a randomised, double-blind, placebo-controlled withdrawal study of flare prevention by canakinumab. The study consisted of two parts with two independent primary endpoints (successful steroid taper and time to flare). In Part I (open label) 177 patients were enrolled and received 4 mg/kg (up to 300 mg) canakinumab administered every 4 weeks for up to 32 weeks. Patients in Part II (double-blind) received either canakinumab 4 mg/kg or placebo every 4 weeks until 37 flare events occurred.

Corticosteroid dose tapering:
Of the total 128 patients who entered Part I taking corticosteroids, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to flare:
Patients taking canakinumab in Part II had a 64% reduced risk of a flare event as compared to the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75; p=0.0032). Sixty-three of the 100 patients entering Part II, whether assigned to placebo or canakinumab, did not experience a flare over the observation period (up to a maximum of 80 weeks).

Health-related and quality of life outcomes in studies G2305 and G2301
Treatment with canakinumab resulted in clinically relevant improvements in patients' physical function and quality of life. In study G2305, the Childhood Health Assessment Questionnaire Least Squares means improvement was 0.69 for canakinumab vs placebo representing 3.6 times the minimal clinically important difference of 0.19 (p=0.0002). The median improvement from baseline to end of Part I of study G2301 was 0.88 (79%). Statistically significant improvements in the Child Health Questionnaire-PF50 scores were reported for canakinumab vs placebo in study G2305 (physical p=0.0012; psychosocial well-being p=0.0017).

Pooled efficacy analysis
Data from the first 12 weeks of canakinumab treatment from studies G2305, G2301 and the extension study were pooled to assess maintenance of efficacy. These data showed similar improvements from baseline to week 12 in the adapted paediatric ACR responses and its components to those observed in the placebo controlled study (G2305). At week 12, the adapted paediatric ACR30, 50, 70, 90 and 100 responses were: 70%, 69%, 61%, 49% and 30%, respectively and 28% of patients had inactive disease (N=178).

Although limited, evidence from the clinical trials suggests that patients not responding to tocilizumab or anakinra may respond to canakinumab.

Study G2301E1
The efficacy observed in the studies G2305 and G2301 was maintained in the open-label long-term extension study G2301E1. Of the 270 SJIA patients in the study, 147 patients had received treatment with canakinumab in studies G2305 or G2301 (Cohort I), and 123 patients were canakinumab-naive patients (Cohort II). Patients in Cohort I were treated for a median duration of 3.2 years (up to 5.2 years), and patients in Cohort II were treated for a median duration of 1.8 years (up to 2.8 years). In the extension study, all patients received canakinumab 4 mg/kg (up to maximum 300 mg) every 4 weeks. In both cohorts, patients who were well-controlled responders (retrospectively defined as adapted paediatric ACR $\geq$ 90) and who did not require a concomitant corticosteroid were permitted to reduce their canakinumab dose to 2 mg/kg every 4 weeks (62/270; 23%).

Study G2306
Study G2306 was an open-label study to assess maintenance of treatment response with canakinumab dose reduction (2 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 8 weeks) in SJIA patients who were receiving canakinumab 4 mg/kg every 4 weeks. Seventy five patients aged 2 to 22 years who maintained inactive disease status for at least 6 consecutive months (clinical remission) with canakinumab monotherapy, including patients who were able to maintain inactive disease status with discontinuation of concomitant corticosteroid and/or methotrexate use for at least 4 weeks, were randomised to receive canakinumab 2 mg/kg every 4 weeks (N=38) or canakinumab 4 mg/kg every 8 weeks (N=37). After 24 weeks, 71% (27/38) of patients who received the reduced dose (2 mg/kg every 4 weeks) and 84% (31/37) of patients who received the prolonged dosing interval (4 mg/kg every 8 weeks) were able to maintain inactive disease status for 6 months. Of the patients in clinical remission who continued with further dose reduction (1 mg/kg every 4 weeks) or dose interval prolongation (4 mg/kg every 12 weeks), 93% (26/28) and 91% (30/33) of patients, respectively, were able to maintain inactive disease status for 6 months. Patients who maintained inactive disease status for 6 additional months at this lowest dose regimen were allowed to discontinue canakinumab. Overall, 33% (25/75) of patients randomised to dose reduction or dose interval prolongation arms were able to discontinue treatment with canakinumab and maintain inactive disease status for 6 months. The rate of adverse events in both treatment arms was similar to the rate seen in patients treated with canakinumab 4 mg/kg every 4 weeks.

AOSD
The efficacy of canakinumab 4 mg/kg (up to maximum 300 mg) administered every 4 weeks in AOSD patients in a randomised, double-blind placebo-controlled study in 36 patients (22 to 70 years old) was comparable to that observed in SJIA patients. In study GDE01T, a higher proportion of patients (12/18, 66.7%) in the canakinumab group than in the placebo group (7/17, 41.2%) demonstrated an improvement from baseline in Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28-ESR) of > 1.2 at week 12, which failed to reach statistical significance (odds ratio 2.86, treatment difference [%] 25.49 [95% CI: 9.43, 55.80]). By week 4, 7 of 18 patients (38.9%) treated with canakinumab had already achieved DAS28-ESR remission versus 2 of 17 patients (11.8%) on placebo. These data are consistent with the results of a pooled efficacy analysis of 418 SJIA patients which showed that the efficacy of canakinumab in a subset of SJIA patients aged 16 to < 20 years (n=34) was consistent with the efficacy observed in patients less than 16 years of age (n=384).

Gouty arthritis
The efficacy of canakinumab for the treatment of acute gouty arthritis attacks was demonstrated in two multicentre, randomised, double-blind, active-controlled studies in patients with frequent gouty arthritis (≥ 3 attacks in the previous 12 months) unable to use NSAIDs or colchicine (due to contraindication, intolerance or lack of efficacy). The studies were 12 weeks followed by 12-week double-blind extension. A total of 225 patients were treated with subcutaneous canakinumab 150 mg and 229 patients were treated with intramuscular triamcinolone acetonide (TA) 40 mg at study entry, and when experiencing a new attack thereafter. The mean number of gouty arthritis attacks in the previous 12 months was 6.5. Over 85% of patients had comorbidity, including hypertension (60%), diabetes (15%), ischaemic heart disease (12%), and stage ≥ 3 chronic kidney disease (25%). Approximately one-third of the patients enrolled (76 [33.8%] in the canakinumab group and 84 [36.7%] in the triamcinolone acetonide group) had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. Concomitant treatment with ULTs was reported by 42% of patients at entry.

The co-primary endpoints were: (i) gouty arthritis pain intensity (visual analogue scale, VAS) at 72 hours post-dose, and (ii) time to first new gouty arthritis attack.

For the overall study population, pain intensity was statistically significantly lower for canakinumab 150 mg compared with triamcinolone acetonide at 72 hours. Canakinumab also reduced the risk of subsequent attacks (see Table 5).

Efficacy results in a subgroup of patients unable to use both NSAIDs and colchicine and who were on ULT, failed ULT or had a contraindication to ULT (N=101) were consistent with the overall study population with a statistically significant difference compared to triamcinolone acetonide in pain intensity at 72 hours (-10.2 mm, p=0.0208) and in reduction of risk of subsequent attacks (Hazard ratio 0.39, p=0.0047 at 24 weeks).

Efficacy results for a more stringent subgroup limited to current users of ULT (N=62) are presented in Table 5. Treatment with canakinumab induced a reduction of pain and reduced the risk of subsequent attacks in patients using ULT and unable to use both NSAIDs and colchicine, although the observed treatment difference compared to triamcinolone acetonide was less pronounced than with the overall study population.

Table 5 Efficacy for the overall study population and in a subgroup of patients currently using ULT and unable to use both NSAIDs and colchicine

Efficacy endpoint	**Overall study population; N=454**	**Unable to use both NSAIDs and colchicine; on ULT N=62**
Treatment of gouty arthritis attacks as measured by pain intensity (VAS) at 72 h		
Least Squares mean estimated difference to triamcinolone acetonide	-10.7	-3.8
CI	(-15.4, -6.0)	(-16.7, 9.1)
p-value, 1-sided	p < 0.0001*	p=0.2798
Risk reduction of subsequent gouty arthritis attacks as measured by time to first new flare (24 weeks)		
Hazard ratio to triamcinolone acetonide	0.44	0.71
CI	(0.32, 0.60)	(0.29, 1.77)
p-value, 1-sided	p < 0.0001*	p=0.2337
* Denotes significant p-value ≤ 0.025		

Safety results showed an increased incidence of adverse events for canakinumab compared to triamcinolone acetonide, with 66% vs 53% of patients reporting any adverse event and 20% vs 10% of patients reporting an infection adverse event over 24 weeks.

Elderly population
Overall, the efficacy, safety and tolerability profile of canakinumab in elderly patients ≥ 65 years of age was comparable to patients < 65 years of age.

Patients on urate lowering therapy (ULT)
In clinical studies, canakinumab has been safely administered with ULT. In the overall study population, patients on ULT had a less pronounced treatment difference in both pain reduction and reduction in the risk of subsequent gouty arthritis attacks compared to patients not on ULT.

Immunogenicity

Antibodies against canakinumab were observed in approximately 1.5%, 3% and 2% of the patients treated with canakinumab for CAPS, SJIA and gouty arthritis, respectively. No neutralising antibodies were detected. No apparent correlation of antibody development to clinical response or adverse events was observed.

There were no antibodies against canakinumab observed in TRAPS, HIDS/MKD and FMF patients treated with doses of 150 mg and 300 mg over 16 weeks of treatment.

Paediatric population

The Marketing Authorisation Holder has completed four Paediatric Investigation Plans for canakinumab (for CAPS, SJIA, FMF – HIDS/MKD and TRAPS respectively). This product information has been updated to include the results of studies with canakinumab in the paediatric population.

The European Medicines Agency has waived the obligation to submit the results of studies with canakinumab in all subsets of the paediatric population in gouty arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

CAPS

Absorption
The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single subcutaneous administration of 150 mg in adult CAPS patients. The mean terminal half-life was 26 days. Mean values for C_{max} and AUC_{inf} after a single subcutaneous dose of 150 mg in a typical adult CAPS patient (70 kg) were 15.9 µg/ml and 708 µg*d/ml. The absolute bioavailability of subcutaneously administered canakinumab was estimated to be 66%. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as intravenous infusion or from 150 to 600 mg as subcutaneous injection. Predicted steady-state exposure values ($C_{min,ss}$, $C_{max,ss}$, $AUC_{,ss,8w}$) after 150 mg subcutaneous administration (or 2 mg/kg, respectively) every 8 weeks were slightly higher in the weight category 40-70 kg (6.6 µg/ml, 24.3 µg/ml, 767 µg*d/ml) compared to the weight categories < 40 kg (4.0 µg/ml, 19.9 µg/ml, 566 µg*d/ml) and > 70 kg (4.6 µg/ml, 17.8 µg/ml, 545 µg*d/ml). The expected accumulation ratio was 1.3-fold following 6 months of subcutaneous administration of 150 mg canakinumab every 8 weeks.

Distribution
Canakinumab binds to serum IL-1 beta. The distribution volume (V_{ss}) of canakinumab varied according to body weight. It was estimated to be 6.2 litres in a CAPS patient of body weight 70 kg.

Elimination
The apparent clearance (CL/F) of canakinumab increases with body weight. It was estimated to be 0.17 l/d in a CAPS patient of body weight 70 kg and 0.11 l/d in a SJIA patient of body weight 33 kg. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS and SJIA patients.

There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender or age-related pharmacokinetic differences were observed after correction for body weight.

TRAPS, HIDS/MKD and FMF

Bioavailability in TRAPS, HIDS/MKD and FMF patients has not been determined independently. Apparent clearance (CL/F) in the TRAPS, HIDS/MKD and FMF population at body weight of 55 kg (0.14 l/d) was comparable to CAPS population at body weight of 70 kg (0.17 l/d). The apparent volume of distribution (V/F) was 4.96 l at body weight of 55 kg.

After repeated subcutaneous administration of 150 mg every 4 weeks, canakinumab minimal concentration at week 16 (C_{min}) was estimated to be 15.4 ± 6.6 µg/ml. The estimated steady state AUC_{tau} was 636.7 ± 260.2 µg*d/ml.

Still's disease (SJIA and AOSD)

Bioavailability in SJIA patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the SJIA and CAPS population (0.004 l/d per kg). The apparent volume of distribution per kg (V/F per kg) was 0.14 l/kg. Sparse pharmacokinetics (PK) data in AOSD patients suggest similar PK of canakinumab as compared to SJIA and other patient populations.

After repeated administration of 4 mg/kg every 4 weeks the accumulation ratio of canakinumab was 1.6 fold in SJIA patients. Steady state was reached after 110 days. The overall predicted mean (±SD) for $C_{min,ss}$, $C_{max,ss}$ and $AUC_{,ss4w}$ were 14.7±8.8 µg/ml, 36.5 ± 14.9 µg/ml and 696.1 ± 326.5 µg*d/ml, respectively.

The AUC_{ss4w} in each age group was 692, 615, 707 and 742 µg*d/ml for 2-3, 4-5, 6-11, and 12-19 years old, respectively. When stratified by weight, a lower (30-40%) median of exposure for $C_{min,ss}$ (11.4 vs 19 µg/ml) and AUC_{ss} (594 vs 880 µg*d/ml) for the lower bodyweight category (≤ 40 kg) vs the higher bodyweight category (> 40 kg) was observed.

Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in young adult SJIA patients aged 16 to 20 years were similar to those in patients less than 16 years of age. Predicted canakinumab steady state exposures at a dose level of 4 mg/kg (maximum 300 mg) in patients over the age of 20 years were comparable to those in SJIA patients younger than 20 years of age.

Gouty arthritis population

Bioavailability in gouty arthritis patients has not been determined independently. Apparent clearance per kg body weight (CL/F per kg) was comparable between the gouty arthritis and CAPS population (0.004 l/d/kg). Mean exposure in a typical gouty arthritis patient (93 kg) after a single subcutaneous 150 mg dose (C_{max}: 10.8 µg/ml and AUC_{inf}: 495 µg*d/ml) was lower than in a typical 70 kg CAPS patient (15.9 µg/ml and 708 µg*d/ml). This is consistent with the observed increase in CL/F with body weight.

The expected accumulation ratio was 1.1-fold following subcutaneous administration of 150 mg canakinumab every 12 weeks.

Paediatric population

Peak concentrations of canakinumab occurred between 2 to 7 days (T_{max}) following single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in paediatric patients 4 years of age and older. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Based on the population pharmacokinetic modelling analysis, the pharmacokinetics of canakinumab in children aged 2 to < 4 years were similar to those in patients 4 years of age and older. Subcutaneous absorption rate was estimated to decrease with age and appeared to be fastest in the youngest patients. Accordingly, T_{max} was shorter (3.6 days) in younger SJIA patients (2-3 years) compared to older SJIA patients (12-19 years; T_{max} 6 days). Bioavailability (AUC_{ss}) was not affected.

An additional pharmacokinetics analysis showed that the pharmacokinetics of canakinumab in 6 paediatric CAPS patients under the age of 2 years were similar to the pharmacokinetics in paediatric patients 2-4 years of age. Based on the population pharmacokinetic modelling analysis, the expected exposures after a dose of 2 mg/kg were comparable across the CAPS paediatric age groups, but were approximately 40% lower in paediatric patients of very low body weight (e.g. 10 kg) than in adult patients (150 mg dose). This is consistent with the observations of higher exposure in higher body weight groups in CAPS patients.

In TRAPS, HIDS/MKD and FMF, exposure parameters (trough concentrations) were comparable across age groups from 2 to < 20 years old following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

Pharmacokinetic properties are similar in CAPS, TRAPS, HIDS/MKD, FMF and SJIA paediatric populations.

Elderly population

No change in pharmacokinetic parameters based on clearance or volume of distribution were observed between elderly patients and adult patients < 65 years of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cross-reactivity, repeated dose toxicity, immunotoxicity, toxicity to reproduce and development.

Formal carcinogenicity studies have not been conducted with canakinumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Histidine
Histidine hydrochloride monohydrate
Polysorbate 80
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

3 years.

From a microbiological point of view, the product should be used immediately after first opening.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Solution for injection in a vial (type I glass) with a stopper (laminated chlorobutyl rubber) and flip-off cap (aluminium).

Packs containing 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ilaris 150 mg/ml solution for injection is supplied in a single-use vial for individual use.

Instructions for administration

Allow the vial to warm to room temperature before injection. The solution should be practically free of visible particles and clear to opalescent. The solution should be colourless or may have a slight brownish-yellow tint. Using an 18 G or 21 G x 2 inch needle (or similar as available on the market) and a 1 ml syringe, carefully withdraw the required volume depending on the dose to be administered. Once the required volume is withdrawn, recap and remove the withdrawal needle from the syringe and attach a 27 G x 0.5 inch needle (or similar as available on the market) to immediately inject the solution subcutaneously.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2009
Date of latest renewal: 06 June 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER 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. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharma S.A.S.
Centre de Biotechnologie
8, rue de l'Industrie
68330 Huningue
France

Name and address of the manufacturer responsible for batch release

Powder for solution for injection
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Solution for injection
Novartis Farmacéutica, S.A.
Gran Vía de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Verovskova Ulica 57
1526 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

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.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Ilaris are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Patient Reminder Card

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single 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

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 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

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

Multipack: 4 (4x1) vials.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single 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

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 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

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg powder for solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection

1 vial. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single 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

The reconstituted solution should ideally be used immediately, but can still be used for up to 24 hours if stored in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package 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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg powder for solution for injection
canakinumab
SC after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

UNIT PACK CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ilaris 150 mg/ml solution for injection
canakinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg canakinumab in 1 ml of solution.

3. LIST OF EXCIPIENTS

Also contains: mannitol, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
Single 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

Use immediately after first opening.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/564/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ilaris 150 mg/ml

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

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilaris 150 mg/ml injection
canakinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ilaris 150 mg powder for solution for injection
canakinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is
Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to a group of medicines called interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases.

What Ilaris is used for
Ilaris is used for treatment of the following inflammatory diseases:
- Periodic fever syndromes:
  - Cryopyrin-associated periodic syndromes (CAPS),
  - Tumour necrosis factor receptor associated periodic syndrome (TRAPS),
  - Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD),
  - Familial Mediterranean fever (FMF).
- Still’s disease including adult onset Still’s disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA)
- Gouty arthritis

More information on each of these diseases is given below.

Periodic fever syndromes

Ilaris is used in adults and children aged 2 years and older to treat the following:

- Cryopyrin-associated periodic syndromes (CAPS) – this is a group of auto-inflammatory diseases, which include:
  - Muckle-Wells syndrome (MWS),
  - Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological, cutaneous, articular syndrome (CINCA),
  - Severe forms of familial cold auto-inflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS)
- Hyperimmunoglobulin D syndrome (HIDS) also known as mevalonate kinase deficiency (MKD)
- Familial Mediterranean fever (FMF): Ilaris is used to treat FMF. Ilaris can be used together with colchicine, if appropriate.

In patients with periodic fever syndromes (CAPS, TRAPS, HIDS/MKD and FMF), the body produces too much IL-1 beta. This may cause fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may improve these symptoms.

Still's disease

Ilaris is used in adults, adolescents and children to treat active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including SJIA and AOSD is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammation. Ilaris blocks the activity of IL-1 beta, which may improve the signs and symptoms of Still's disease.

Gouty arthritis

Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the formation of urate crystals. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

2. What you need to know before you use Ilaris

Do not use Ilaris
- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active and severe infection.

Warning and precautions
Talk to your doctor before using Ilaris if any of the following applies to you:
– if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
– if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may check whether you have tuberculosis using a specific test.
– if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
– if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also "Other medicines and Ilaris").

Contact your doctor immediately
- If you have ever developed an atypical, widespread rash or skin peeling after taking Ilaris. The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjuction with high body temperature and enlarged lymph nodes.

<u>Still's disease</u>
– Patients with Still's disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still's disease (flare).

Children and adolescents
– **CAPS, TRAPS, HIDS/MKD, FMF and SJIA**: Ilaris can be used in children aged 2 years and older.
– **Gouty arthritis**: Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines and Ilaris
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
– Live vaccines: You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while you are being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, discuss this with your doctor. A live vaccine should normally be given 3 months after your last injection of Ilaris and 3 months before the next one.
– Medicines called tumour necrosis factor (TNF) inhibitors, such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risks of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines
Ilaris treatment may give you a spinning sensation (dizziness or vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

How much Ilaris to use
<u>Cryopyrin-associated periodic syndromes (CAPS)</u>
The recommended starting dose of Ilaris is:
- *Adults and children aged 4 years or more*
  - 150 mg for patients who weigh more than 40 kg
  - 2 mg/kg for patients who weigh between 15 kg and 40 kg
  - 4 mg/kg for patients who weigh between 7.5 kg and less than 15 kg
- *Children aged 2 or 3 years*
  - 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to the second dose, your treatment will be continued with 300 mg or 4 mg/kg every 8 weeks.
- If you do not respond well enough to the second dose, a third dose of Ilaris at 300 mg or 4 mg/kg may be given.
- If you respond well enough to the third dose, your treatment will be continued at 600 mg or 8 mg/kg every 8 weeks.

For children given a starting dose of 4 mg/kg who have not responded well enough after 7 days, the doctor may give a second dose of 4 mg/kg. If the child responds well enough to this, treatment may be continued with a dose of 8 mg/kg every 8 weeks.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and familial Mediterranean fever (FMF)
The recommended starting dose of Ilaris is:

- *Adults and children aged 2 years or more*
  - 150 mg for patients who weigh more than 40 kg
  - 2 mg/kg for patients who weigh between 7.5 kg and less than 40 kg

Ilaris is injected every 4 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to this, your treatment will be continued with 300 mg or 4 mg/kg every 4 weeks.

Still's disease (SJIA and AOSD)
The recommended dose of Ilaris for patients with Still's disease with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is injected every 4 weeks as a single dose.

Gouty arthritis
Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a patient with Ilaris
If you are a patient with CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), or a caregiver of a patient with one of these conditions, you may administer Ilaris injections yourself after proper training in the correct injection technique.

- The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
- The doctor or nurse will demonstrate how to administer Ilaris injections.
- Do not try to administer an injection yourself if you have not been properly trained or if you are not sure how to do it.
- Ilaris 150 mg powder for solution for injection is supplied in a single-use vial for individual use.
- Never re-use the leftover solution.

For instructions on how to administer Ilaris injections, please read the section "Instructions for use" at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris

- **CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA)**: You should continue using Ilaris for as long as the doctor tells you.
- **Gouty arthritis**: If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should
If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris
If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you stop using Ilaris
Stopping your treatment with Ilaris may cause your condition to get worse. Do not stop taking Ilaris unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:
- Fever lasting longer than 3 days or any other symptoms that might suggest a serious infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to a serious infection, an unusual infection (opportunistic infection) or be related to low levels of white blood cells (called leukopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:
Very common (may affect more than 1 in 10 people):
- Infections of any kind. These can include:
  - Respiratory infections such as chest infection, flu, sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks or forehead with or without fever (pneumonia, bronchitis, influenza, sinusitis, rhinitis, pharyngitis, tonsilitis, nasopharyngitis, upper respiratory tract infection).
  - Other infections such as ear infection, skin infection (cellulitis), stomach pain and feeling sick (gastroenteritis) and painful and frequent urination with or without fever (urinary tract infection).
- Upper abdominal pain.
- Pain in joints (arthralgia).
- Drop in level of white blood cells (leukopenia).
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):
– Candida - vaginal yeast infection (vulvovaginal candidiasis).
– Feeling dizzy, spinning sensation (dizziness or vertigo).
– Pain in the back or muscles.
– Feeling weak or very tired (fatigue, asthenia).
– Drop in level of white blood cells which help prevent infection (neutropenia).
– Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
– Abnormal liver function test results (transaminases increased) or high level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).

Uncommon (may affect up to 1 in 100 people):
– Heartburn (gastro-oesophageal reflux disease).
– Drop in level of blood cells which help prevent bleeding (platelets).

Tell your doctor or your child's doctor immediately if you notice any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Ilaris

- Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

- Store in a refrigerator (2°C - 8°C). Do not freeze.

- Store in the original package in order to protect from light.

- After mixing (reconstitution) the medicine should be used immediately. If not used immediately, the solution should be stored in the refrigerator (2°C - 8°C) and used within 24 hours.

- Do not use this medicine if you notice that the solution is not clear to opalescent or contains particles.

- Any unused medicine must be discarded after the dose has been injected.

- 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 Ilaris contains
- The active substance is canakinumab. One vial of powder contains 150 mg canakinumab. After reconstitution, each ml of solution contains 150 mg canakinumab.
- The other ingredients are: sucrose, histidine, histidine hydrochloride monohydrate, polysorbate 80.

What Ilaris looks like and contents of the pack
- Ilaris is supplied as a powder for solution for injection (150 mg in a 6 ml glass vial).
- The powder is white.
- Ilaris is available in packs containing one vial or multipacks comprising four intermediate packs, each containing one vial. Not all pack sizes may be marketed in your country.

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Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharma GmbH
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Slovenija
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Suomi/Finland
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Novartis Sverige AB
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Novartis Ireland Limited
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Instructions for use of Ilaris powder for solution for injection

Please note that the preparation of the injection takes about 30 minutes.
See also section 3, "Injecting Ilaris yourself or injecting a patient with Ilaris".

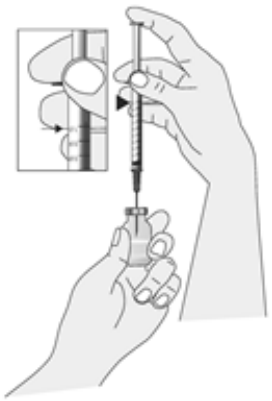
Read these instructions all the way through before beginning.

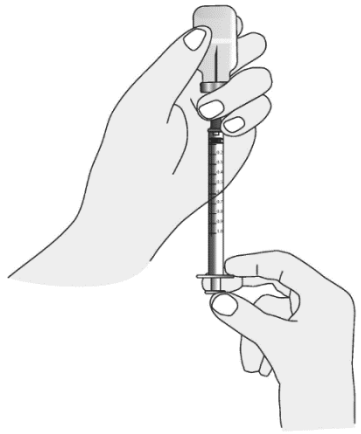
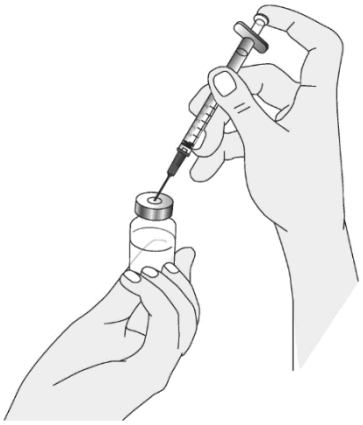
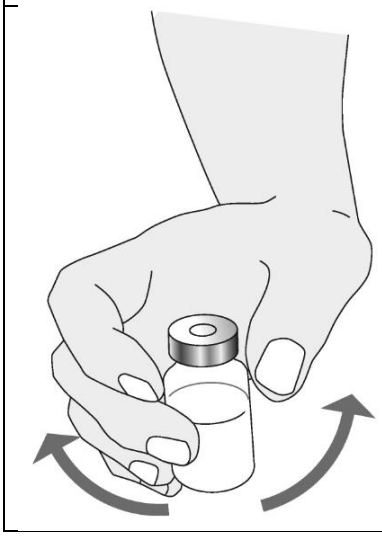
Essential preparation
- Find a clean place in which to prepare and administer the injection.
- Wash your hands with soap and water.
- Check the expiry dates on the vial and syringes. Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Always use new, unopened needles and syringes. Avoid touching the needles and the tops of the vials.

Gather together the necessary items
Included in the pack
- one vial of Ilaris powder for solution for injection (keep refrigerated)

Not included in the pack
- one vial (or ampoule) of sterile water for injections ("water") (at room temperature)
- one 1.0 ml syringe
- one 18 G x 2 inch (50 mm) needle for reconstituting the powder ("transfer needle")
- one 27 G x 0.5 inch (13 mm) needle for injecting ("injection needle")
- alcohol swabs
- clean, dry cotton swabs
- an adhesive plaster
- a proper disposal container for used needles, syringe and vials (sharps container)

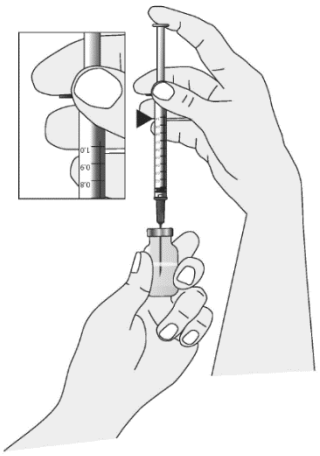
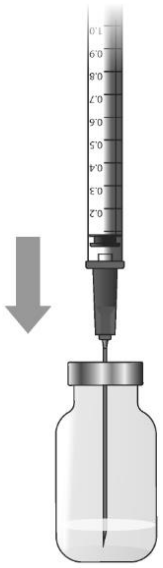
Mixing Ilaris

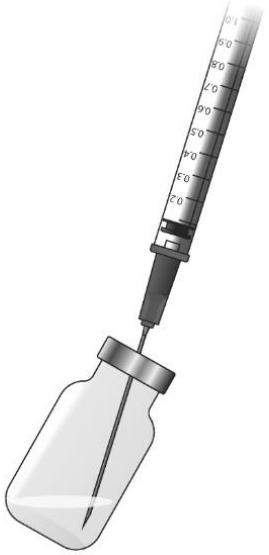
	1. Remove the caps from the Ilaris and water vials. Do not touch the vial stoppers. Clean the stoppers with the alcohol swab. 2. Open the wrappers containing the syringe and the transfer needle (the 50 mm needle) and attach the needle to the syringe. 3. Carefully remove the cap from the transfer needle and set the cap aside. Pull the plunger all the way down to the 1.0 ml mark, filling the syringe with air. Insert the needle into the water vial through the centre of the rubber stopper. 4. Gently push the plunger all the way down until air is in the vial.

	5. Turn the vial and syringe upside down and bring to eye level. 6. Make sure the tip of the transfer needle is covered by the water and slowly pull the syringe plunger down to slightly past the 1.0 ml mark. If you see bubbles in the syringe, remove bubbles as instructed by your healthcare professional or pharmacist. 7. Make sure 1.0 ml of water is in the syringe, then take the needle out of the vial. (There will be water remaining in the vial.)
	8. Insert the transfer needle through the centre of the stopper of the vial of Ilaris powder, taking care not to touch the needle or the stopper. Slowly inject the water into the vial containing the Ilaris powder. 9. Carefully remove the transfer needle from the vial and recap the needle as instructed by your healthcare provider or pharmacist.
	10. Without touching the rubber stopper, swirl (do not shake) the vial slowly at an angle of about 45 degrees for about 1 minute. Allow to stand for 5 minutes.

	11. Now, gently turn the vial upside down and back again ten times, again taking care not to touch the rubber stopper. 12. Allow to stand for about 15 minutes at room temperature to get a clear to opalescent solution. Do not shake. Do not use if particles are present in the solution. 13. Make sure all of the solution is in the bottom of the vial. If drops remain on the stopper, tap the side of the vial to remove them. The solution should be clear to opalescent and free of visible particles. The solution should be colourless or may have a slight brownish-yellow tint. - If not used immediately after mixing, the solution should be stored in the refrigerator (2°C to 8°C) and used within 24 hours.

Preparing the injection

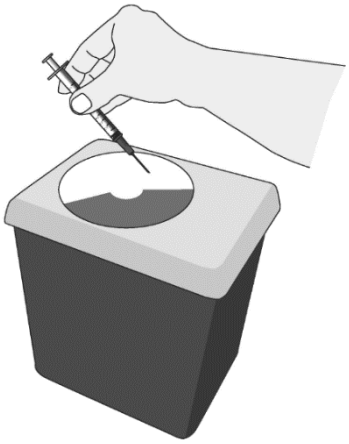
	14. Clean the rubber stopper of the vial containing the Ilaris solution with a new alcohol swab. 15. Uncap the transfer needle again. Pull the plunger of the syringe all the way down to the 1.0 ml mark, filling the syringe with air. Insert the syringe needle into the vial of Ilaris solution through the centre of the rubber stopper. The needle should not be in the liquid at this point. Gently push the plunger all the way down until all of the air is injected into the vial. Do not inject air into the liquid.
	16. **Do not** turn the vial and syringe upside down, the vial should stay upright. Insert the needle all the way into the vial until it reaches the bottom edge.

	17. Tip the vial to ensure that the required amount of solution can be drawn into the syringe 18. NOTE: The required amount depends on the dose to be administered. Your healthcare provider will instruct you on the right amount for you. 19. Slowly pull the syringe plunger up to the correct mark (amount to be given), filling the syringe with Ilaris solution. If there are air bubbles in the syringe, remove bubbles as instructed by your healthcare provider. Ensure that the correct amount of solution is in the syringe. 20. Remove the syringe and needle from the vial. (There may be solution remaining in the vial.) Recap the transfer needle as instructed by your healthcare provider or pharmacist. Remove the transfer needle from the syringe. Place the transfer needle in the sharps container. 21. Open the wrapper containing the injection needle and attach the needle to the syringe. Set the syringe aside.

Giving the injection

	22. Choose an injection site on the upper thigh, abdomen, upper arm or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Do not inject into scar-tissue as this may mean you do not get all of your medicine. Avoid injecting into a vein. 23. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle. 24. Gently pinch the skin up at the injection site. Hold the syringe at a 90-degree angle and in a single, smooth motion, push the needle straight down completely into the skin.
	25. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.

After the injection

	26. Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops. Then apply an adhesive plaster.
	27. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist. Never re-use syringes or needles. 28. Properly dispose of vials containing remaining water and Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Any unused product or waste material should be disposed of in accordance with local requirements. Keep the sharps container out of reach of children. Dispose of it as directed by your healthcare provider or pharmacist.

Package leaflet: Information for the user

Ilaris 150 mg/ml solution for injection
canakinumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ilaris is and what it is used for
2. What you need to know before you use Ilaris
3. How to use Ilaris
4. Possible side effects
5. How to store Ilaris
6. Contents of the pack and other information

1. What Ilaris is and what it is used for

What Ilaris is
Ilaris contains the active substance canakinumab, a monoclonal antibody that belongs to a group of medicines called interleukin inhibitors. It blocks the activity of a substance called interleukin-1 beta (IL-1 beta) in the body, which is present at increased levels in inflammatory diseases.

What Ilaris is used for
Ilaris is used for treatment of the following inflammatory diseases:
- Periodic fever syndromes:
  - Cryopyrin-associated periodic syndromes (CAPS),
  - Tumour necrosis factor receptor associated periodic syndrome (TRAPS),
  - Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD),
  - Familial Mediterranean fever (FMF).
- Still’s disease including adult onset Still’s disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA)
- Gouty arthritis

More information on each of these diseases is given below.

Periodic fever syndromes

Ilaris is used in adults and children aged 2 years and older to treat the following:

- Cryopyrin-associated periodic syndromes (CAPS) – this is a group of auto-inflammatory diseases, which include:
  - Muckle-Wells syndrome (MWS),
  - Neonatal-onset multisystem inflammatory disease (NOMID), also called chronic infantile neurological, cutaneous, articular syndrome (CINCA),
  - Severe forms of familial cold auto-inflammatory syndrome (FCAS) / familial cold urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS)
- Hyperimmunoglobulin D syndrome (HIDS) also known as mevalonate kinase deficiency (MKD)
- Familial Mediterranean fever (FMF): Ilaris is used to treat FMF. Ilaris can be used together with colchicine, if appropriate.

In patients with periodic fever syndromes (CAPS, TRAPS, HIDS/MKD and FMF), the body produces too much IL-1 beta. This may cause fever, headache, fatigue, skin rash, or painful joints and muscles. By blocking the activity of IL-1 beta, Ilaris may improve these symptoms.

Still's disease

Ilaris is used in adults, adolescents and children to treat active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older if other treatments have not worked well enough. Ilaris can be used alone or in combination with methotrexate.

Still's disease including SJIA and AOSD is an inflammatory disease that can cause pain, swelling and inflammation of one or more joints, as well as rash and fever. A pro-inflammatory protein called IL-1 beta plays an important role in Still's disease inflammation. Ilaris blocks the activity of IL-1 beta, which may improve the signs and symptoms of Still's disease.

Gouty arthritis

Ilaris is used in adults to treat the symptoms of frequent gouty arthritis attacks if other treatments have not worked well enough.

Gouty arthritis is caused by the formation of urate crystals. These crystals cause excessive production of IL-1 beta, which in turn can lead to sudden, severe pain, redness, warmth and swelling in a joint (known as a gouty arthritis attack). By blocking the activity of IL-1 beta, Ilaris may lead to an improvement in these symptoms.

2. What you need to know before you use Ilaris

Do not use Ilaris
- if you are allergic to canakinumab or any of the other ingredients of this medicine (listed in section 6).
- if you have, or suspect you have, an active and severe infection.

Warning and precautions
Talk to your doctor before using Ilaris if any of the following applies to you:
– if you currently have an infection or if you have had repeated infections or a condition such as a known low level of white blood cells which makes you more likely to get infections.
– if you have or have ever had tuberculosis or direct contact with a person with an active tuberculosis infection. Your doctor may check whether you have tuberculosis using a specific test.
– if you have signs of a liver disorder such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
– if you need to have any vaccinations. You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while being treated with Ilaris (see also "Other medicines and Ilaris").

Contact your doctor immediately
- If you have ever developed an atypical, widespread rash or skin peeling after taking Ilaris. The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Ilaris treatment, predominantly in patients with systemic juvenile idiopathic arthritis (sJIA). Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjuction with high body temperature and enlarged lymph nodes.

<u>Still's disease</u>
– Patients with Still's disease may develop a condition called macrophage activation syndrome (MAS), which can be life-threatening. Your doctor will monitor you for potential triggering factors of MAS that include infections and re-activation of the underlying Still's disease (flare).

Children and adolescents
– **CAPS, TRAPS, HIDS/MKD, FMF and SJIA**: Ilaris can be used in children aged 2 years and older.
– **Gouty arthritis**: Ilaris is not recommended for children or adolescents under 18 years of age.

Other medicines and Ilaris
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.
– Live vaccines: You are advised to avoid being vaccinated with a type of vaccine called a live vaccine while you are being treated with Ilaris. Your doctor may want to check your vaccination history and give you any vaccinations that you have missed before you start treatment with Ilaris. If you need to be given a live vaccine after starting treatment with Ilaris, discuss this with your doctor. A live vaccine should normally be given 3 months after your last injection of Ilaris and 3 months before the next one.
– Medicines called tumour necrosis factor (TNF) inhibitors, such as etanercept, adalimumab or infliximab. These are used mainly in rheumatic and autoimmune diseases. They should not be used with Ilaris because this may increase the risk of infections.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- You are advised to avoid becoming pregnant and must use adequate contraception while using Ilaris and for at least 3 months after the last Ilaris treatment. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risks of taking Ilaris during pregnancy.
- If you received canakinumab while you were pregnant, it is important that you inform the baby's doctor or nurse before any vaccinations are given to your baby. Your baby should not receive live vaccines until at least 16 weeks after you received your last dose of canakinumab before giving birth.
- It is not known whether Ilaris passes into human milk. Your doctor will discuss with you the potential risks of taking Ilaris before breast-feeding.

Driving and using machines
Ilaris treatment may give you a spinning sensation (dizziness or vertigo) or intense tiredness (asthenia). This may affect your ability to drive or use tools or machines. If you feel a spinning sensation or feel tired, do not drive or use any tools or machines until you are feeling normal again.

3. How to use Ilaris

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Keep your doctor informed of your condition and any symptoms before you use or are given Ilaris (see section 2). Your doctor may decide to delay or interrupt your treatment, but only if necessary.

Ilaris is intended for subcutaneous use. This means that it is injected through a short needle into the fatty tissue just under the skin.

If you have gouty arthritis, your treatment will be overseen by a doctor with specialist training. Ilaris should be injected by a healthcare professional only.

If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), you may inject yourself with Ilaris after proper training, or a caregiver may inject it for you.

How much Ilaris to use
<u>Cryopyrin- associated periodic syndromes (CAPS)</u>
The recommended starting dose of Ilaris is:
- *Adults and children aged 4 years or more*
  - 150 mg for patients who weigh more than 40 kg
  - 2 mg/kg for patients who weigh between 15 kg and 40 kg
  - 4 mg/kg for patients who weigh between 7.5 kg and less than 15 kg
- *Children aged 2 or 3 years*
  - 4 mg/kg for patients with body weight of 7.5 kg or more

Ilaris is injected every 8 weeks as a single dose.

– If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
– If you respond well enough to the second dose, your treatment will be continued with 300 mg or 4 mg/kg every 8 weeks.
– If you do not respond well enough to the second dose, a third dose of Ilaris at 300 mg or 4 mg/kg may be given.
– If you respond well enough to the third dose, your treatment will be continued at 600 mg or 8 mg/kg every 8 weeks.

For children given a starting dose of 4 mg/kg who have not responded well enough after 7 days, the doctor may give a second dose of 4 mg/kg. If the child responds well enough to this, treatment may be continued with a dose of 8 mg/kg every 8 weeks.

Tumour necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and familial Mediterranean fever (FMF)
The recommended starting dose of Ilaris is:
- *Adults and children aged 2 years or more*
    - 150 mg for patients who weigh more than 40 kg
    - 2 mg/kg for patients who weigh between 7.5 kg and less than 40 kg

Ilaris is injected every 4 weeks as a single dose.

- If you have not responded well enough to the treatment after 7 days, your doctor may give you another dose of 150 mg or 2 mg/kg.
- If you respond well enough to this, your treatment will be continued with 300 mg or 4 mg/kg every 4 weeks.

Still's disease (SJIA and AOSD)
The recommended dose of Ilaris for patients with Still's disease with body weight of 7.5 kg and above is 4 mg/kg (up to a maximum of 300 mg). Ilaris is injected every 4 weeks as a single dose.

Gouty arthritis
Your doctor will discuss with you the need to start or adjust a urate lowering therapy to lower the uric acid level in your blood.

The recommended dose of Ilaris for adult gouty arthritis patients is 150 mg given as a single dose at the time of a gouty arthritis attack.

If you need another treatment with Ilaris, and got relief from the last dose, you must wait at least 12 weeks before the next dose.

Injecting Ilaris yourself or injecting a patient with Ilaris
If you are a patient with CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA), or a caregiver of a patient with one of these conditions, you may administer Ilaris injections yourself after proper training in the correct injection technique.
– The patient or caregiver and the doctor should decide together who will administer the Ilaris injections.
– The doctor or nurse will demonstrate how to administer Ilaris injections.
– Do not try to administer an injection yourself if you have not been properly trained or if you are not sure how to do it.
– Ilaris 150 mg/ml solution for injection is supplied in a single-use vial for individual use.
– Never re-use the leftover solution.

For instructions on how to administer Ilaris injections, please read the section "Instructions for use" at the end of this leaflet. If you have any questions, talk to your doctor, pharmacist or nurse.

How long to use Ilaris
- **CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA)**: You should continue using Ilaris for as long as the doctor tells you.
- **Gouty arthritis**: If you have a gouty arthritis attack, you will be given a single dose of Ilaris. If you experience a new attack, your doctor may consider giving you a new dose of Ilaris but not earlier than 12 weeks from the previous dose.

If you use more Ilaris than you should
If you accidentally inject more Ilaris than the recommended dose, it is unlikely to be serious, but you should inform your doctor, pharmacist or nurse as soon as possible.

If you forget to use Ilaris
If you have CAPS, TRAPS, HIDS/MKD, FMF or Still's disease (AOSD or SJIA) and have forgotten to inject a dose of Ilaris, inject the next dose as soon as you remember. Then talk to the doctor to discuss when you should inject the next dose. You should then continue with injections at the recommended intervals as before.

If you stop using Ilaris
Stopping your treatment with Ilaris may cause your condition to get worse. Do not stop taking Ilaris unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor immediately, if you notice any of the side effects below:
- Fever lasting longer than 3 days or any other symptoms that might suggest a serious infection. These include shivering, chills, malaise, loss of appetite, body aches, typically in connection with a sudden onset of illness, sore throat or mouth ulcers, cough, phlegm, chest pain, difficulty breathing, ear pain, prolonged headache or localised redness, warmth or swelling of your skin or inflammation of connective tissue (cellulitis). These symptoms could be due to a serious infection, an unusual infection (opportunistic infection) or be related to low levels of white blood cells (called leukopenia or neutropenia). Your doctor may check your blood regularly if considered necessary.
- Allergic reactions with rash and itching and possibly also hives, difficulty breathing or swallowing, dizziness, unusual awareness of your heart beat (palpitations) or low blood pressure.

Other side effects of Ilaris include:
Very common (may affect more than 1 in 10 people):
- Infections of any kind. These can include:
  - Respiratory infections such as chest infection, flu, sore throat, runny nose, blocked nose, sneezing, feeling of pressure or pain in the cheeks or forehead with or without fever (pneumonia, bronchitis, influenza, sinusitis, rhinitis, pharyngitis, tonsilitis, nasopharyngitis, upper respiratory tract infection).
  - Other infections such as ear infection, skin infection (cellulitis), stomach pain and feeling sick (gastroenteritis) and painful and frequent urination with or without fever (urinary tract infection).
- Upper abdominal pain.
- Pain in joints (arthralgia).
- Drop in level of white blood cells (leukopenia).
- Abnormal kidney function test results (creatinine renal clearance decreased, proteinuria).
- Injection site reaction (such as redness, swelling, warmth and itching).

Common (may affect up to 1 in 10 people):
- Candida - vaginal yeast infection (vulvovaginal candidiasis).
- Feeling dizzy, spinning sensation (dizziness or vertigo).
- Pain in the back or muscles.
- Feeling weak or very tired (fatigue, asthenia).
- Drop in level of white blood cells which help prevent infection (neutropenia).
- Abnormal levels of triglycerides in your blood (lipid metabolism disorder).
- Abnormal liver function test results (transaminases increased) or high level of bilirubin in the blood, with or without yellow skin and eyes (hyperbilirubinaemia).

Uncommon (may affect up to 1 in 100 people):
- Heartburn (gastro-oesophageal reflux disease).
- Drop in level of blood cells which help prevent bleeding (platelets).

Tell your doctor or your child’s doctor immediately if you notice any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Ilaris

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- The solution should be used immediately after first piercing the vial stopper to prepare the injection.
- Do not use this medicine if you notice that the solution is not clear to opalescent or contains particles.
- Any unused medicine must be discarded after withdrawal of the dose.
- 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 Ilaris contains

– The active substance is canakinumab. One vial contains 150 mg canakinumab in 1 ml of solution.
– The other ingredients are mannitol, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections.

What Ilaris looks like and contents of the pack

– Ilaris is supplied as a solution for injection in a 2 ml glass vial.
– The solution is a clear to opalescent liquid. It is colourless to slightly brownish-yellow. Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown.
– Ilaris is available in packs containing one vial.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Instructions for use of Ilaris solution for injection

Read all the way through these instructions before injecting.
- It is important not to try to inject yourself until you have been trained by your healthcare professional.
- See also section 3, "Injecting Ilaris yourself or injecting a patient with Ilaris".

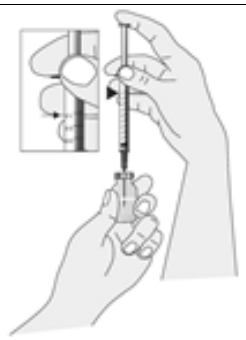
Essential preparation
- Find a clean place in which to prepare and give yourself the injection.
- Wash your hands with soap and water, then dry them on a clean towel.
- After removing the vial from the refrigerator, check the expiry date on the vial. Do not use after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.
- Let the vial stand unopened for 10 minutes to bring the contents to room temperature. Do not try to heat the vial. Let it warm up on its own.
- Always use new, unopened needles and syringes. Do not touch the needles or the top of the vial.

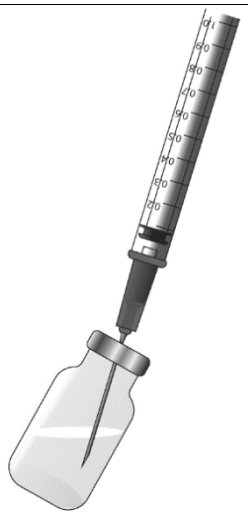
Gather together the necessary items

Included in the pack
- one vial of Ilaris solution for injection (keep refrigerated)

Not included in the pack
- one 1.0 ml syringe
- one needle (such as 18 G or 21 G x 2 inch or similar, as available on the market) to draw up the solution from the vial ("withdrawal needle").
- one 27 G x 0.5 inch (or similar, as available on the market) needle for injecting ("injection needle")
- alcohol swabs
- clean, dry cotton swabs
- an adhesive plaster
- a proper disposal container for used needles, syringe and vial (sharps container)

Preparing the injection

	1. Take off the protective cap from the Ilaris vial. Do not touch the vial stopper. Clean the rubber stopper of the vial with an alcohol swab. Open the wrappers containing the syringe and the withdrawal needle. - Put the withdrawal needle on the syringe. - Take off the cap from the withdrawal needle. - Push the withdrawal needle into the vial of Ilaris solution through the centre of the rubber stopper.

	2. Tip the vial to ensure that the required amount of solution can be drawn into the syringe. NOTE: The required amount depends on the dose to be administered. Your healthcare provider will instruct you on the right amount for you. 3. Slowly pull the syringe plunger up to the correct mark (amount to be given as per healthcare provider's instructions), filling the syringe with Ilaris solution. If there are air bubbles in the syringe, remove bubbles as instructed by your healthcare provider. Ensure that the correct amount of solution is in the syringe. 4. Remove the syringe and withdrawal needle from the vial. (There may be solution remaining in the vial.) Recap the withdrawal needle as instructed by your healthcare provider or pharmacist. Remove the withdrawal needle from the syringe and place it in the sharps container. 5. Open the wrapper containing the injection needle and attach the needle to the syringe. Immediately proceed to administering the injection.

Giving the injection

	6. Choose an injection site on the upper thigh, abdomen, upper arm or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Do not inject into scar tissue as this may mean you do not get all of your medicine. Avoid injecting into a vein. 7. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle. 8. Gently pinch the skin up at the injection site. Hold the syringe at a 90-degree angle and in a single, smooth motion, push the needle straight down completely into the skin.
	9. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.

After the injection

	10. Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops. Then apply an adhesive plaster.
	11. Safely dispose of needles and syringe in the sharps container or as directed by your healthcare provider or pharmacist. Never re-use syringes or needles. 12. Properly dispose of vials containing remaining Ilaris solution (if any) as directed by your healthcare provider or pharmacist. Any unused product or waste material should be disposed of in accordance with local requirements. Never re-use the leftover solution. Keep the sharps container out of reach of children. Dispose of it as directed by your healthcare provider or pharmacist.

「既存治療で効果不十分な成人発症スチル病」を効能又は効果として承認されている医薬品はないが，効能又は効果及び薬理作用の類似性の観点から「成人スチル病」を効能又は効果として承認されている生物製剤を同種同効薬に選定した。なお，本申請に伴う本剤の追加部分は下線で示した。

販売名	イラリス皮下注射液 150 mg	[アクテムラ点滴静注用 80 mg，アクテムラ点滴静注用 200 mg， アクテムラ点滴静注用 400 mg]
一般名	カナキヌマブ（遺伝子組換え）	トシリズマブ（遺伝子組換え）
会社名	ノバルティスファーマ株式会社	中外製薬株式会社
効能又は効果	○以下のクリオピリン関連周期性症候群 ・家族性寒冷自己炎症症候群 ・マックル・ウェルズ症候群 ・新生児期発症多臓器系炎症性疾患 ○高 IgD 症候群（メバロン酸キナーゼ欠損症） ○TNF 受容体関連周期性症候群 既存治療で効果不十分な下記疾患 ○家族性地中海熱 ○全身型若年性特発性関節炎 ○成人発症スチル病	○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）、多関節に活動性を有する若年性特発性関節炎、全身型若年性特発性関節炎、成人スチル病 ○キャッスルマン病に伴う諸症状及び検査所見（C 反応性タンパク高値、フィブリノーゲン高値、赤血球沈降速度亢進、ヘモグロビン低値、アルブミン低値、全身倦怠感）の改善。ただし、リンパ節の摘除が適応とならない患者に限る。 ○悪性腫瘍治療に伴うサイトカイン放出症候群 ○SARS-CoV-2 による肺炎（ただし、酸素投与を要する患者に限る）
添付文書の改訂日	2021 年 11 月改訂（第 2 版）に追記	2023 年 9 月改訂（第 4 版）

＊＊2023年9月改訂（第4版、効能変更、用法及び用量変更）
＊2023年4月改訂

貯　　法：2～8℃保存
有効期間：30箇月

日本標準商品分類番号
876399

ヒト化抗ヒトIL-6レセプターモノクローナル抗体 トシリズマブ（遺伝子組換え）注

生物由来製品、劇薬、処方箋医薬品注）

	80mg	200mg	400mg
承認番号	22000AMX01593	21900AMX01337	22000AMX01594
販売開始	2008年6月	2005年6月	2008年6月

アクテムラ®点滴静注用80mg
アクテムラ®点滴静注用200mg
アクテムラ®点滴静注用400mg
ACTEMRA® for Intravenous Infusion

CHUGAI
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注）注意－医師等の処方箋により使用すること

1．警告

〈効能共通〉

1.1 感染症

本剤投与により、敗血症、肺炎等の重篤な感染症があらわれ、致命的な経過をたどることがある。本剤はIL-6の作用を抑制し治療効果を得る薬剤である。IL-6は急性期反応（発熱、CRP増加等）を誘引するサイトカインであり、本剤投与によりこれらの反応は抑制されるため、感染症に伴う症状が抑制される。そのため感染症の発見が遅れ、重篤化することがあるので、本剤投与中は患者の状態を十分に観察し問診を行うこと。症状が軽微であり急性期反応が認められないときでも、白血球数、好中球数の変動に注意し、感染症が疑われる場合には、胸部X線、CT等の検査を実施し、適切な処置を行うこと。［2.3、8.4、8.10、9.1.1、11.1.2参照］

1.2 治療開始に際しては、重篤な感染症等の副作用があらわれることがあること及び本剤が疾病を完治させる薬剤でないことも含めて患者に十分説明し、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本剤を投与すること。

1.3 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。

〈関節リウマチ及び多関節に活動性を有する若年性特発性関節炎〉

1.4 本剤の治療を行う前に、少なくとも1剤の抗リウマチ薬の使用を十分勘案すること。［5.1参照］

2．禁忌（次の患者には投与しないこと）

〈効能共通〉

2.1 活動性結核の患者［症状を悪化させるおそれがある。］［8.5、9.1.3、11.1.2参照］

2.2 本剤の成分に対し過敏症の既往歴のある患者

〈SARS-CoV-2による肺炎を除く効能〉

2.3 重篤な感染症を合併している患者［感染症が悪化するおそれがある。］［1.1、8.4、8.10、9.1.1、11.1.2参照］

3．組成・性状

3.1 組成

販売名	アクテムラ点滴静注用80mg	アクテムラ点滴静注用200mg	アクテムラ点滴静注用400mg
有効成分	1バイアル（4mL）中トシリズマブ（遺伝子組換え）注）80mg	1バイアル（10mL）中トシリズマブ（遺伝子組換え）注）200mg	1バイアル（20mL）中トシリズマブ（遺伝子組換え）注）400mg
添加剤	1バイアル（4mL）中精製白糖　200mg ポリソルベート80　2mg リン酸水素ナトリウム水和物　適量 リン酸二水素ナトリウム水和物　適量	1バイアル（10mL）中精製白糖　500mg ポリソルベート80　5mg リン酸水素ナトリウム水和物　適量 リン酸二水素ナトリウム水和物　適量	1バイアル（20mL）中精製白糖　1000mg ポリソルベート80　10mg リン酸水素ナトリウム水和物　適量 リン酸二水素ナトリウム水和物　適量

注）本剤は、チャイニーズハムスター卵巣細胞を用いて製造される。

＊3.2 製剤の性状

販売名	アクテムラ点滴静注用80mg	アクテムラ点滴静注用200mg	アクテムラ点滴静注用400mg
剤形	注射剤（バイアル）		
性状	無色～微黄色の液		
pH	6.3～6.7		
浸透圧比	0.5～0.8 （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
関節リウマチ（関節の構造的損傷の防止を含む）、多関節に活動性を有する若年性特発性関節炎、全身型若年性特発性関節炎、成人スチル病

○キャッスルマン病に伴う諸症状及び検査所見（C反応性タンパク高値、フィブリノーゲン高値、赤血球沈降速度亢進、ヘモグロビン低値、アルブミン低値、全身倦怠感）の改善。ただし、リンパ節の摘除が適応とならない患者に限る。

○悪性腫瘍治療に伴うサイトカイン放出症候群

○SARS-CoV-2による肺炎（ただし、酸素投与を要する患者に限る）

5．効能又は効果に関連する注意

〈関節リウマチ及び多関節に活動性を有する若年性特発性関節炎〉

5.1 過去の治療において、少なくとも1剤の抗リウマチ薬による適切な治療を行っても、効果不十分な場合に投与すること。［1.4参照］

〈全身型若年性特発性関節炎及び成人スチル病〉

5.2 過去の治療において、副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。

5.3 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MASを合併している患者ではMASに対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中にMASが発現した場合は、投与を中止し、速やかにMASに対する適切な治療を行うこと。

〈悪性腫瘍治療に伴うサイトカイン放出症候群〉

＊＊5.4 本剤の投与にあたっては、学会のガイドライン等の最新の情報を参考に適応患者を選択し、その他の対症療法の実施とともに使用すること。

〈SARS-CoV-2による肺炎〉

5.5 酸素投与、人工呼吸器管理又は体外式膜型人工肺（ECMO）導入を要する患者を対象に入院下で投与を行うこと。

5.6 海外医師主導臨床試験は室内気 SpO_2が92%未満又は酸素投与中でCRP値7.5mg/dL以上のSARS-CoV-2による肺炎患者を対象として実施され、副腎皮質ステロイド薬併用下で本剤の有効性が確認されている[1)]。当該試験の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。

＊＊6. 用法及び用量

〈関節リウマチ及び多関節に活動性を有する若年性特発性関節炎〉

通常、トシリズマブ（遺伝子組換え）として1回8mg/kgを4週間隔で点滴静注する。

〈全身型若年性特発性関節炎、成人スチル病及びキャッスルマン病〉

通常、トシリズマブ（遺伝子組換え）として1回8mg/kgを2週間隔で点滴静注する。なお、症状により1週間まで投与間隔を短縮できる。

〈悪性腫瘍治療に伴うサイトカイン放出症候群〉

通常、トシリズマブ（遺伝子組換え）として体重30kg以上は1回8mg/kg、体重30kg未満は1回12mg/kgを点滴静注する。

〈SARS-CoV-2による肺炎〉

通常、成人には、副腎皮質ステロイド薬との併用において、トシリズマブ（遺伝子組換え）として1回8mg/kgを点滴静注する。症状が改善しない場合には、初回投与終了から8時間以上の間隔をあけて、トシリズマブ（遺伝子組換え）として8mg/kgを1回追加投与できる。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 血清中トシリズマブ濃度が維持されない状態で投与を継続すると、抗トシリズマブ抗体が発現する可能性が高くなるため、用法・用量を遵守すること。

7.2 本剤と他の抗リウマチ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。

〈全身型若年性特発性関節炎及び成人スチル病〉

7.3 症状改善が不十分であり、かつC反応性タンパク（CRP）を指標としてIL-6作用の抑制効果が不十分と判断される場合に限り、投与間隔を短縮できる。

〈キャッスルマン病〉

7.4 投与毎にCRPを測定し、症状改善が不十分と判断される場合に限り、CRPを指標として投与間隔を短縮できる。

〈SARS-CoV-2による肺炎〉

7.5 海外医師主導臨床試験では副腎皮質ステロイド薬を併用していない患者において本剤投与により全死亡割合が高くなる傾向が認められた[1)]。

7.6 バリシチニブとの併用について、有効性及び安全性は確立していない。

8. 重要な基本的注意

〈効能共通〉

8.1 本剤投与中はアナフィラキシーショック、アナフィラキシーに対する適切な薬物治療（アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬等）や緊急処置を直ちに実施できるようにしておくこと。また、投与終了後も症状のないことを確認すること。［11.1.1参照］

8.2 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。

8.3 抗リウマチ生物製剤による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。［9.1.2参照］

8.4 本剤投与により、急性期反応（発熱、CRP増加等）、感染症状が抑制され、感染症発見が遅れる可能性があるため、急性期反応が認められないときでも、白血球数、好中球数を定期的に測定し、これらの変動及び喘鳴、咳嗽、咽頭痛等の症状から感染症が疑われる場合には、胸部X線、CT等の検査を実施し適切な処置を行うこと。また、呼吸器感染のみならず皮膚感染や尿路感染等の自他覚症状についても注意し、異常が見られる場合には、速やかに担当医師に相談するよう、患者を指導すること。［1.1、2.3、8.10、9.1.1、11.1.2参照］

8.5 本剤投与に先立って結核に関する十分な問診（結核の既往歴、結核患者との濃厚接触歴等）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。

本剤投与中は、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、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）には速やかに担当医師に連絡するよう説明すること。なお、結核の活動性が確認された場合は本剤を投与せず、結核の治療を優先すること。［2.1、9.1.3、11.1.2参照］

8.6 本剤投与中は、生ワクチン接種により感染するおそれがあるので、生ワクチン接種は行わないこと。

8.7 臨床試験において胸膜炎（感染症が特定できなかったものを含む）が報告されている。治療期間中に胸膜炎（所見：胸水貯留、胸部痛、呼吸困難等）が認められた場合には、その病因を十分に鑑別し、感染症でない場合も考慮して適切な処置を行うこと。

8.8 総コレステロール値、トリグリセリド値、LDLコレステロール値の増加等の脂質検査値異常があらわれることがあるので、投与開始3カ月後を目安に、以後は必要に応じて脂質検査を実施し、臨床上必要と認められた場合には、高脂血症治療薬の投与等の適切な処置を考慮すること。

8.9 臨床試験において心障害が認められていることから、患者の状態を十分に観察し、必要に応じて心電図検査、血液検査、胸部エコー等を実施すること。［9.1.8、11.1.6参照］

〈SARS-CoV-2による肺炎を除く効能〉

8.10 感染症を合併している患者に本剤を投与することにより、感染症が重篤化するおそれがあるため、投与開始に際しては、肺炎等の感染症の有無を確認すること。なお、SARS-CoV-2による肺炎を除く適応疾患の臨床症状（発熱、悪寒、倦怠感、リンパ節腫脹等）は感染症の症状と類似しているため、鑑別を十分に行うこと。［1.1、2.3、8.4、9.1.1、11.1.2参照］

8.11 他の抗リウマチ生物製剤から本剤に切り替える際には、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。

〈全身型若年性特発性関節炎、成人スチル病及びキャッスルマン病〉

8.12 本剤を休薬・中止する際には、IL-6の作用が過剰に発現し病態が悪化する可能性が否定できないので、必要に応じて副腎皮質ステロイド薬の追加・増量等の適切な処置を考慮すること。

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（SARS-CoV-2による肺炎の場合はSARS-CoV-2による肺炎を除く、その他の効能の場合は重篤な感染症は除く）を合併している患者又は感染症が疑われる患者

〈効能共通〉

感染症を合併している場合は感染症の治療を優先すること。感染症が悪化するおそれがある。［1.1、2.3、8.4、8.10、11.1.2参照］

〈悪性腫瘍治療に伴うサイトカイン放出症候群、SARS-CoV-2による肺炎〉

治療上の有益性と危険性を考慮し、治療方針を十分に検討すること。

9.1.2 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抗体又はHBs抗体陽性）

最新のB型肝炎治療ガイドラインを参考に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。抗リウマチ生物製剤を投与された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。［8.3参照］

9.1.3 結核の既感染者（特に結核の既往歴のある患者及び胸部X線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) 結核の既感染者では、結核を活動化させる可能性が否定できない。［2.1、8.5、11.1.2参照］

(2) 結核の既往歴を有する場合及び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。以下のいずれかの患者には、原則として本剤の投与開始前に適切に抗結核薬を投与すること。［2.1、8.5、11.1.2参照］

・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

9.1.4 易感染性の状態にある患者

投与を避けることが望ましい。なお、リンパ球数減少が遷延化した場合（目安として500/μL）は、投与を開始しないこと。日和見感染を含む感染症を誘発するおそれがある。

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。[11.1.3参照]

9.1.6 腸管憩室のある患者

[11.1.4参照]

9.1.7 白血球減少、好中球減少、血小板減少のある患者

白血球減少、好中球減少、血小板減少が更に悪化するおそれがある。[11.1.5参照]

9.1.8 心疾患を合併している患者

定期的に心電図検査を行いその変化に注意すること。臨床試験において心障害が認められている。[8.9、11.1.6参照]

9.3 肝機能障害患者

トランスアミナーゼ値上昇に注意するなど観察を十分に行うこと。[10.2、11.1.7、15.1.2参照]

9.5 妊婦

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。カニクイザルにおいて本薬は胎盤関門を通過することが報告されている。

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。本薬のヒト乳汁への移行は不明である。

9.7 小児等

〈SARS-CoV-2による肺炎を除く効能〉

低出生体重児、新生児又は乳児を対象とした臨床試験は実施していない。

〈SARS-CoV-2による肺炎〉

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

患者の状態を十分に観察しながら慎重に投与すること。一般に生理機能が低下している。

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
肝機能障害を起こす可能性のある薬剤 抗リウマチ薬(DMARD) [9.3、11.1.7、15.1.2参照]	肝機能障害があらわれることがある。	機序不明

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 アナフィラキシーショック(0.1%)、**アナフィラキシー**(0.1%)

血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、瘙痒感、潮紅等があらわれることがあるので、異常が認められた場合には直ちに投与を中止し、アドレナリン、副腎皮質ステロイド薬、抗ヒスタミン薬を投与するなど適切な処置を行うとともに症状が回復するまで患者の状態を十分に観察すること。[8.1参照]

11.1.2 感染症

肺炎(3.3%)、帯状疱疹(2.0%)、感染性胃腸炎(0.7%)、蜂巣炎(1.4%)、感染性関節炎（0.5%）、敗血症（0.6%）、非結核性抗酸菌症(0.4%)、結核（0.1%）、ニューモシスチス肺炎（0.3%）等の日和見感染を含む重篤な感染症があらわれ、致命的な経過をたどることがある。[1.1、2.1、2.3、8.4、8.5、8.10、9.1.1、9.1.3参照]

11.1.3 間質性肺炎（0.5%）

関節リウマチ患者では、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X線、CT及び血液ガス検査等を実施し、本剤の投与を中止するとともにニューモシスチス肺炎との鑑別診断（β-D-グルカンの測定等）を考慮に入れ適切な処置を行うこと。[9.1.5参照]

11.1.4 腸管穿孔（0.2%）

本剤投与により、憩室炎等の急性腹症の症状（腹痛、発熱等）が抑制され、発見が遅れて穿孔に至る可能性があるため、異常が認められた場合には、腹部X線、CT等の検査を実施するなど十分に観察し、適切な処置を行うこと。[9.1.6参照]

11.1.5 無顆粒球症（0.1%未満）、**白血球減少**（4.5%）、**好中球減少**（1.6%）、**血小板減少**（2.1%）

[9.1.7参照]

11.1.6 心不全（0.2%）

[8.9、9.1.8参照]

11.1.7 肝機能障害（頻度不明）

AST、ALT、ビリルビン等の上昇を伴う肝機能障害があらわれることがある。[9.3、10.2、15.1.2参照]

11.2 その他の副作用

	1%以上	0.1～1%未満	0.1%未満
抵抗機構	ヘルペスウイルス感染	インフルエンザ、口腔カンジダ症、耳下腺炎、創傷感染	
呼吸器	上気道感染〔鼻咽頭炎、上気道炎等〕(10.7%)、気管支炎、咽喉頭疼痛	咳嗽、副鼻腔炎、鼻炎、鼻漏、胸膜炎、喀血、喘息、咽頭不快感、咽頭紅斑、鼻閉、鼻出血	気管支拡張症
代謝	コレステロール増加（4.9%）、トリグリセリド増加、高脂血症、高コレステロール血症、LDL増加	LDH上昇、HDL増加、高トリグリセリド血症、血中尿酸増加、CK上昇、総蛋白減少、糖尿病増悪、血中カリウム減少、血糖増加、血中リン増加、血清フェリチン減少	血中リン減少、血中カルシウム減少
肝臓	肝機能異常、ALT上昇、AST上昇	γ-GTP上昇、ビリルビン増加、Al-P上昇、脂肪肝、胆石症	
循環器	高血圧	血圧上昇、血圧低下、動悸、T波逆転、T波振幅減少、上室性期外収縮、心室性期外収縮	ST部分上昇、ST部分下降、T波振幅増加
血液・凝固		リンパ球数減少、貧血、白血球数増加、フィブリノゲン減少、好酸球数増加、フィブリン分解産物〔FDP、Dダイマー〕増加、ヘマトクリット減少、ヘモグロビン減少、リンパ節炎、リンパ節腫脹、好中球数増加、赤血球数減少	ＴＡＴ増加
消化器	口内炎、下痢、胃腸炎、腹痛	悪心、便秘、嘔吐、腹部不快感、口唇炎、腹部膨満、食欲不振、胃・腸ポリープ、逆流性食道炎、痔核、消化不良、舌炎、胃潰瘍、急性膵炎	口渇
		歯周病、齲歯、歯痛	
精神神経	頭痛	浮動性めまい、感覚減退、不眠症、末梢性ニューロパシー	
耳		中耳炎、眩暈、突発難聴、外耳炎、耳鳴	耳不快感

	1%以上	0.1～1%未満	0.1%未満
眼		結膜炎、麦粒腫、眼乾燥、結膜出血、霰粒腫、白内障、眼瞼炎	硝子体浮遊物、網膜出血
皮膚	発疹〔湿疹、痒疹、丘疹等〕、瘙痒症、白癬、皮膚感染	爪感染、蕁麻疹、紅斑、皮膚潰瘍、皮下出血、嵌入爪、ざ瘡、皮膚乾燥、水疱、角化症、脱毛症、皮膚嚢腫	
筋・骨格		関節痛、背部痛、筋痛〔筋痛、肩こり〕、四肢痛、骨粗鬆症、骨密度減少、頚部痛、若年性関節炎増悪	
泌尿器		膀胱炎、尿路感染、BUN増加、尿中赤血球陽性、腎盂腎炎、尿糖、尿蛋白、腎結石、NAG増加、頻尿	尿中白血球陽性
生殖器		腟感染、性器出血	子宮頚管ポリープ
その他	膿瘍、発熱	浮腫、倦怠感、免疫グロブリンG減少、胸痛、胸部不快感、季節性アレルギー、CRP増加、悪寒、潮紅、アレルギー性鼻炎、気分不良、ほてり、注射部位反応〔紅斑、腫脹、血腫、疼痛、静脈炎、発疹等〕、血栓性静脈炎、DNA抗体陽性[注1)]、体重増加、抗核抗体陽性[注1)]	リウマチ因子陽性、発汗障害

注1）関節リウマチ第Ⅲ相2試験でのDNA抗体の推移は、217例において陰性化10例（4.6%）、陽性化0例である。抗核抗体の推移は216例において陰性化24例（11.1%）、陽性化18例（8.3%）である。

注2）副作用の発現頻度は製造販売後調査を含む。

14．適用上の注意

14.1 薬剤調製時の注意

14.1.1 希釈時及び希釈後に泡立つような激しい振動を与えないこと。本剤はポリソルベートを含有しているので、泡立ちやすい。

14.1.2 用時調製し、調製後は速やかに使用すること。また、残液は廃棄すること。

14.1.3 希釈方法

本剤の各バイアル中のトシリズマブ濃度は20mg/mLである。患者の体重から換算した必要量を体重25kg以下の場合は50mL、25kgを超える場合は100～250mLの日局生理食塩液に加え、希釈する。

<<体重あたりの換算式>>

$$\text{抜き取り量（mL）} = \frac{\text{体重（kg）} \times 8\ (\text{mg/kg})^{注)}}{20\ (\text{mg/mL})}$$

注）悪性腫瘍治療に伴うサイトカイン放出症候群患者で体重30kg未満の場合は12mg/kgとする。

14.2 薬剤投与時の注意

14.2.1 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）を用い独立したラインにて投与すること。

14.2.2 他の注射剤、輸液等と混合しないこと。

14.2.3 投与開始時は緩徐に点滴静注を行い、患者の状態を十分に観察し、異常がないことを確認後、点滴速度を速め1時間程度で投与する。

15．その他の注意

15.1 臨床使用に基づく情報

15.1.1 本剤投与により抗トシリズマブ抗体が発現したとの報告がある（国内臨床試験・疾患別、関節リウマチ：601例中18例（3.0%）、多関節に活動性を有する若年性特発性関節炎：19例中1例（5.3%）、全身型若年性特発性関節炎：128例中11例（8.6%）［以上、効能追加時］、キャッスルマン病：35例中1例（2.9%）［承認時］）。

15.1.2 本邦において、本剤と抗リウマチ薬（DMARD）との併用療法における有効性及び安全性は確立していない。なお、海外の関節リウマチを対象とした臨床試験では、トランスアミナーゼ値上昇の発現頻度が本剤単剤療法時に比べてDMARD併用療法時で高かった。基準値の3倍を超えるALTあるいはAST上昇の発現頻度は、DMARD併用療法：本剤8mg/kg+DMARD群103/1582例（6.5%）、プラセボ+DMARD群18/1170例（1.5%）、単剤療法：本剤8mg/kg群6/288例（2.1%）、MTX単剤群14/284例（4.9%）で、これらの異常は一過性で肝炎や肝不全に伴うものではなかった。［9.3、10.2、11.1.7参照］

15.1.3 国内の臨床試験では2.9年（投与期間0.1～8.1年の中央値）まで、海外の関節リウマチを対象とした臨床試験では4.6年（投与期間0.0～5.8年の中央値）までの期間で実施されており、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。

15.1.4 関節リウマチを対象とした本剤の海外臨床試験において、本剤8mg/kg投与時の重篤な感染症の発現頻度が体重100kgを超える患者群で高い傾向が認められたため、海外における1回投与量の上限は800mgとされている。

15.1.5 関節リウマチを対象とした海外臨床試験において、本剤との因果関係は不明であるが脱髄関連疾患が認められたとの報告がある。

15.1.6 海外の関節リウマチ患者を対象とした二重盲検比較試験における悪性腫瘍の発現率は、本剤投与群では1.60/100人・年（95%信頼区間：1.04-2.37、投与期間の中央値：0.5年、被験者数：2,644例、延べ投与：1,560人・年）、比較対照薬投与群（メトトレキサートあるいはDMARD）では1.48/100人・年（95%信頼区間：0.74-2.65、投与期間の中央値：0.5年、被験者数：1,454例、延べ投与：743人・年）であった。二重盲検比較試験を含む海外長期継続投与試験における悪性腫瘍の発現率は、1.62/100人・年（投与期間の中央値：4.6年、被験者数：4,009人、延べ投与：14,994人・年）であった[2)]（外国人データ）。

15.2 非臨床試験に基づく情報

15.2.1 動物実験（マウス）において、gp130を介したシグナル伝達が心筋細胞の保護作用を有することが報告されている[3)]。gp130を介してシグナル伝達に関与するサイトカインは複数知られており、IL-6もその一つである。本薬はIL-6の作用を阻害することから、心臓への影響は否定できない。

15.2.2 本薬はヒトとカニクイザルのIL-6レセプターに対しては中和活性を示すが、マウス及びラットのIL-6レセプターに対しては中和活性を示さない。このため、がん原性試験は実施されていない。

15.2.3 ヒト肝細胞を用いた*in vitro*試験において、IL-6が肝薬物代謝酵素（CYPs）発現を抑制することが報告されていることから[4)-6)]、ヒト肝細胞にIL-6をトシリズマブ共存下で添加したところ、CYPsの発現に変化は認められなかった[7)]。また、炎症反応を有する患者では、IL-6の過剰産生によりCYPsの発現が抑制されているとの報告がある[8),9)]。関節リウマチ患者を対象とした臨床試験において、本剤投与後にIL-6阻害に伴ってCYP3A4、CYP2C19及びCYP2D6発現量が増加することが示唆された。このことから、過剰のIL-6によって抑制されていたCYPsの発現が本剤投与により回復し、炎症反応の改善に伴って併用薬の効果が減弱する可能性は否定できない[10)]。

16．薬物動態

16.1 血中濃度

〈健康成人〉

16.1.1 単回投与

健康成人男性5例を対象に、0.15、0.50、1.0、2.0mg/kg[注1)]を単回投与した（1時間点滴静注）。C_{max}は投与量に比例して上昇したものの、投与量の増加に伴ってCL_{total}は減少し、$t_{1/2}$及びMRTが延長したことから、トシリズマブの体内動態に非線形性が認められた[11)]。

表1　単回投与時の薬物動態パラメータ

投与量 (mg/kg)	C_{max} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d,ss}$ (mL/kg)
0.15	2.4±0.6	11±6	17±16	3.8±2.3	25±22	63.4±16.6
0.50	8.5±1.2	285±73	33± 4	1.3±0.2	47± 5	58.4± 7.1
1.0	19.5±2.7	1009±222	49± 5	0.8±0.1	69± 8	57.3±10.9
2.0	37.6±8.8	2532±569	74± 9	0.6±0.2	107±16	65.9± 8.3

（例数：5、平均値±SD）

注1）本剤の承認用量は、1回8mg/kg（ただし、体重30kg未満の悪性腫瘍治療に伴うサイトカイン放出症候群は1回12mg/kg）である。

〈関節リウマチ〉

16.1.2 単回投与

関節リウマチ患者31例を対象に、8mg/kgを単回投与した（1時間点滴静注）。血清中トシリズマブ濃度を図1に示した。このときの薬物動態パラメータはAUC_{last}= 19852±5749μg・hr/mL（平均値±SD、以下同様）、$t_{1/2}$= 133±25.7hr、CL_{total}=0.4±0.1mL/hr/kg及び$V_{d,ss}$= 78.5±16.8mL/kgであった[12)]。

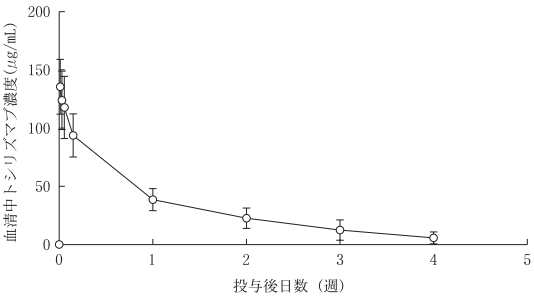


図1　関節リウマチ患者における単回投与時の血清中トシリズマブ濃度推移（平均値±SD）

16.1.3 反復投与

(1) 第Ⅰ/Ⅱ相試験（用量相関性の検討）

関節リウマチ患者15例（1群5例）を対象に、2、4あるいは8mg/kg[注1)]を2週間隔にて投与した（2時間点滴静注）。CL_{total}は投与量の増加にともなって減少し、$t_{1/2}$は延長したことから非線形性の体内動態が認められた[13)]。

表2　関節リウマチ患者における反復投与時の薬物動態パラメータ

投与回数	投与量 (mg/kg)	C_{1hr} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d,ss}$ (mL/kg)
1	2	43.6±10.1	3440± 823	74±18	0.5±0.2	107±25	55.0±13.0
	4	49.0±12.6	4663±2185	97±50	0.9±0.5	138±68	102±24.0
	8	82.5±32.4	10661±4070	160±34	0.6±0.2	227± 46	137±31.6
3	2	27.9±12.3	3014±1070	87±18	0.5±0.1	140±26	70.7±13.5
	4	49.5±10.1	6035±3200	140±71	0.7±0.5	204±105	98.5±14.6
	8	129.9±48.1	19939±8900	242±71	0.3±0.1	343±105	90.9±29.9

（例数：4-5、平均値±SD）

(2) 第Ⅲ相試験

関節リウマチ患者157例を対象に、8mg/kgを4週間隔で13回投与した（1時間点滴静注）。血清中トシリズマブ濃度は初回投与以降上昇し、血清中トシリズマブ投与直前値は3回目投与4週間後（初回投与12週後、平均値±SD以下同様）で9.8±7.5μg/mL、6回目投与4週間後（初回投与24週間後）で12.3±8.6μg/mLであり、初回投与20週後以降ほぼ一定の値で推移した[14)]。

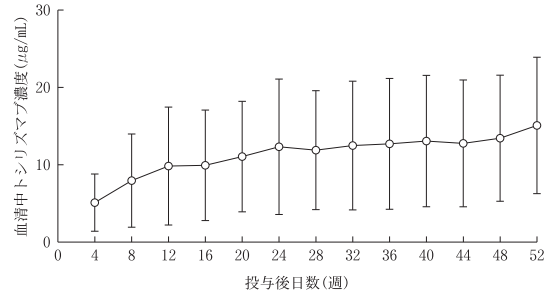


図2　関節リウマチ患者における反復投与時の血清中トシリズマブ濃度（投与直前値）推移（平均値±SD）

〈多関節に活動性を有する若年性特発性関節炎〉

16.1.4 反復投与

多関節に活動性を有する若年性特発性関節炎患者19例（3-19歳、中央値12歳）を対象に、8mg/kgを4週間隔で3回投与した（1時間点滴静注）。初回投与後の血清中トシリズマブ薬物動態パラメータの比較を表3に示した。7歳未満の群で血清中トシリズマブの消失速度の大きい症例が認められた[15)]。

表3　多関節に活動性を有する若年性特発性関節炎患者における反復投与時の薬物動態パラメータ

年齢	C_{1hr} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d,ss}$ (mL/kg)
3-7未満	107.8±15.0	12970±2511	N.A.	N.A.	N.A.	N.A.
7-15未満	158.6±34.4	20878±5328	99±12	0.3±0.0	150± 9	48.0± 7.0
15以上	158.1±36.2	25954±6157	143±43	0.3±0.1	200±49	60.5±12.2
全例	145.0±37.5	25275±6722	123±41	0.3±0.1	178±46	58.3±13.9

（平均値±SD、N.A.：算出せず）

（3-7歳未満：C_{1hr}及びAUC_{last}：n=5、7-15歳未満：C_{1hr}及びAUC_{last}：n=7、その他のパラメータ：n=4、15歳以上：n=7）

〈全身型若年性特発性関節炎〉

16.1.5 反復投与

全身型若年性特発性関節炎患者（2-19歳、中央値8歳）を対象に、8mg/kgを2週間隔で3回反復投与し（1時間点滴静注）、その後有効性の認められた被験者を対象に6回（合計9回、初回投与後18週間）投与を行った。

初回投与後及び3回目投与後の血清中トシリズマブ薬物動態パラメータを表4に示した。7歳未満の群で血清中トシリズマブの消失速度の大きい症例が認められた。

血清中トシリズマブ濃度推移は初回投与8週から14週の範囲で定常状態となったと考えられ、血清中トシリズマブ濃度（投与直前値）は57.4μg/mL（初回投与18週後、例数：13）であった。

低体重、低身長及び低年齢のいずれかの因子を有する患者において、血清中トシリズマブ濃度の消失速度が大きくなることがあった[16)]。

表4　全身型若年性特発性関節炎患者における反復投与時の薬物動態パラメータ

年齢	投与回数	C_{1hr} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d,ss}$ (mL/kg)
2-7未満	1	142.8±31.6	17677±5193	N.A.	N.A.	N.A.	N.A.
	3	171.7±51.2	23706±9704	100±38	0.3±0.1	155±60	45.4±7.6
7-15未満	1	176.7±48.5	24701±7611	N.A.	N.A.	N.A.	N.A.
	3	239.8±70.2	35333±11668	127±26	0.2±0.2	188±49	43.0±17.5
15以上	1	166.0±31.8	23653±3571	N.A.	N.A.	N.A.	N.A.
	3	214.0±40.0	33336±8115	139±30	0.2±0.0	249±21	43.6±11.2

（平均値±SD、N.A.：算出せず）

（2-7歳未満：n=19-23、7-15歳未満：n=25-28、15歳以上：n=4-5）

〈キャッスルマン病〉

16.1.6 反復投与

キャッスルマン病患者28例を対象に、8mg/kgを2週間隔で8回反復投与した（1時間点滴静注）。

血清中トシリズマブ濃度は8回目投与直前値で36.6±17.5μg/mLであり、初回投与以降上昇していた。初回投与後6回目投与まで$t_{1/2}$及びMRTは延長したが、投与6回目以降はほぼ一定の値を示した[17)]。

表5　キャッスルマン病患者における反復投与時の薬物動態パラメータ

投与量 (mg/kg)	投与回数	C_{1hr} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (mL/hr/kg)	MRT (hr)	$V_{d,ss}$ (mL/kg)
8	1	112.9±24.7	13092±3254	99.7±17.1	0.6±0.2	145±26.8	80.1±15.0
	8	192.3±38.7	28423±7410	139±37.4	0.2±0.1	205±54.2	46.8± 8.8

（例数：26-28、平均値±SD）

〈成人スチル病〉

16.1.7 反復投与

成人発症スチル病患者に、8mg/kgを2週間隔で反復投与した（1時間点滴静注）。血清中トシリズマブ濃度は初回投与後10週投与直前値で56.0±27.6μg/mLを示し、10週以降はほぼ一定の値を示した[18]。

表6　成人発症スチル病患者における反復投与時の血清中トシリズマブ濃度

時点	2週	4週	6週	8週	10週	12週
C_{min} (μg/mL)	15.4±8.2 (n=13)	15.7±19.4 (n=13)	29.3±29.6 (n=11)	40.8±25.6 (n=10)	56.0±27.6 (n=9)	57.2±28.1 (n=9)

（平均値±SD）

〈悪性腫瘍治療に伴うサイトカイン放出症候群〉

16.1.8 反復投与

キメラ抗原受容体遺伝子導入T細胞輸注療法に伴うサイトカイン放出症候群43例（日本人1例）を対象に、体重30kg以上の場合は8mg/kg、30kg未満の場合は12mg/kgを投与した（1時間点滴静注）。初回投与時の血清中トシリズマブ濃度のC_{max}は43.2～210μg/mL（日本人：122μg/mL）であった[19]。

〈SARS-CoV-2による肺炎〉

16.1.9 1回又は2回投与

SARS-CoV-2による肺炎患者を対象に、標準治療併用下においてトシリズマブ8mg/kgを1-2回点滴静注した（1回投与につき1時間点滴静注）。血清中トシリズマブ薬物動態パラメータを表7に示した[20]。

表7　SARS-CoV-2による肺炎患者における薬物動態パラメータ

投与量	C_{max} (μg/mL)	AUC_{last} (μg・hr/mL)	$t_{1/2}$ (hr)	CL_{total} (L/hr)	MRT (hr)	$V_{d,ss}$ (L)
8mg/kg 1回投与	160± 27.1	18700± 6090	140± 59.6	0.0285± 0.00833	195± 64.8	5.22± 1.17
8mg/kg 2回投与	254± 54.3	42400± 18000	177± 101	N.A.	264± 124[注2]	N.A.

（平均値±SD、N.A.：算出せず）

（1回投与：n=37-41、2回投与：n=6-7）

注2）2回投与分の血清中トシリズマブ濃度から求めた。

16.5 排泄

健康成人男性5例を対象に、0.15、0.50、1.0、2.0mg/kg[注1]を1時間点滴静注したとき、いずれの投与量においてもトシリズマブは尿中に排泄されず、トシリズマブの主消失クリアランスは腎外クリアランスであることが示された[11]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈関節リウマチ〉

17.1.1 国内第Ⅲ相二重盲検比較試験

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8mg/週+トシリズマブプラセボ（プラセボ群）及びメトトレキサートプラセボ+トシリズマブ8mg/kg/4週（本剤投与群）を24週間投与した二重盲検比較試験を実施した。成績は以下のとおりであった[21]。

・症状の緩和

最終観察時のACR基準#1 20%改善頻度は、プラセボ群25.0%に対し、本剤投与群で80.3%と有意に高かった（P<0.001）。

#1：アメリカリウマチ学会（ACR）の臨床的改善の評価基準

表1　ACR基準20%改善頻度

	プラセボ[注1]	トシリズマブ	P値
例数	64	61	
ACR20	25.0%	80.3%	<0.001

注1）メトトレキサート8mg/週投与

・日常生活動作（ADL）の改善

投与前から最終観察時までの日常生活動作（ADL）の改善をMHAQ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0.01に対し、本剤投与群で0.32と有意に改善した（P<0.001）。なお、MCID（minimum clinically important differences）として定義される0.22を超えて改善を示した症例は、プラセボ群34.4%に対し、本剤投与群で67.2%であり、本剤投与群で有意に多かった（P<0.001）。

副作用発現頻度は、61例中50例（82.0%）であった。主な副作用は、血中コレステロール増加22例（36.1%）、LDL増加17例（27.9%）、血中トリグリセリド増加10例（16.4%）、鼻咽頭炎7例（11.5%）、口内炎5例（8.2%）、LDH増加4例（6.6%）、HDL増加4例（6.6%）、高脂血症4例（6.6%）であった。

17.1.2 国内第Ⅲ相無作為割付群間比較試験

DMARDあるいは免疫抑制剤に効果不十分な関節リウマチ患者を対象とし、トシリズマブ8mg/kg/4週投与又は既存治療（DMARDあるいは免疫抑制剤の治療）を52週間継続する無作為割付群間比較試験を実施した。成績は以下のとおりであった[22]。

・関節の構造的損傷の防止

投与前から52週までの関節破壊進展を手及び足のX線スコア（Modified Sharp Score）で評価した結果を下表に示す。Totalスコアにおいて、既存治療で6.12悪化したのに対して、本剤投与群は2.34であり、有意に関節破壊の進行が抑制された（P=0.001）。

表2　投与52週後のModified Sharp法による各スコアの変化量

	既存治療	トシリズマブ	P値
例数	143	157	
骨びらん	3.21（1.0）	0.85（0.0）	<0.001
関節裂隙狭小化	2.91（1.0）	1.49（0.0）	0.024
Total	6.12（2.5）	2.34（0.5）	0.001

（　）内は中央値

副作用発現頻度は，157例中139例（88.5%）であった。主な副作用は、血中コレステロール増加60例（38.2%）、鼻咽頭炎47例（29.9%）、LDL増加41例（26.1%）、血中トリグリセリド増加20例（12.7%）、ALT増加17例（10.8%）、AST増加14例（8.9%）、下痢11例（7.0%）、γ-GTP増加11例（7.0%）、好中球数減少10例（6.4%）、白血球数減少10例（6.4%）、発疹9例（5.7%）、爪囲炎9例（5.7%）であった。

〈多関節に活動性を有する若年性特発性関節炎〉

17.1.3 国内第Ⅲ相試験

多関節に活動性を有する若年性特発性関節炎患者19例を対象に、トシリズマブ8mg/kgを4週間隔で3回投与した。最終観察時のJIA基準#2 30%、50%、70%改善頻度はそれぞれ、94.7%、94.7%、57.9%であり、原疾患の著明な改善が認められた[23]。

#2：Giannini等[24]により提唱された若年性特発性関節炎（JIA）に対する薬効評価であり標準的な評価基準

副作用発現頻度は、19例中13例（68.4%）であった。副作用は、上気道感染5例（26.3%）、鼻咽頭炎4例（21.1%）、下痢2例（10.5%）、扁桃炎、上気道の炎症、口唇炎、悪心、口内炎、湿疹、発疹、蕁麻疹、尿中血陽性、リンパ球数減少がそれぞれ1例（5.3%）であった。

〈全身型若年性特発性関節炎〉

17.1.4 国内第Ⅲ相試験

全身型若年性特発性関節炎患者56例を対象としてトシリズマブ8mg/kgを2週間隔で3回反復投与するオープン期間にて、JIA基準#2 30%以上の改善を示し、かつCRPが0.5mg/dL未満に改善した解析対象患者43例を対象に、二重盲検比較試験にてトシリズマブ群20例あるいはプラセボ群23例として2週間隔で6回投与し、JIA基準30%以上の改善、かつCRPが1.5mg/dL未満の改善の維持率及び維持期間を比較した。その結果、トシリズマブ群の効果維持率は80.0%であり、プラセボ群（17.4%）に比べて有意に高かった（P<0.001）。また、効果維持期間もトシリズマブ群の方がプラセボ群に比べて有意に長かった（P<0.001）[25]。

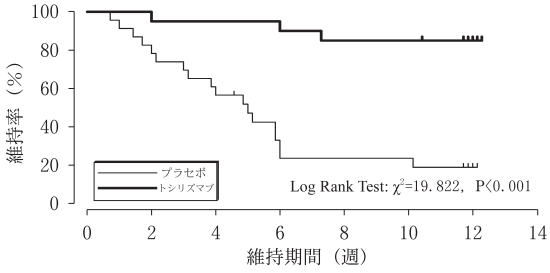


図　効果維持率の推移（Kaplan-Meier曲線）

副作用発現頻度は、56例中53例（94.6%）であった。主な副作用は、鼻咽頭炎15例（26.8%）、ALT増加13例（23.2%）、上気道感染が11例（19.6%）、AST増加8例（14.3%）、血中コレステロール増加8例（14.3%）、咽頭炎7例（12.5%）、胃腸炎6例（10.7%）、嘔吐6例（10.7%）、リンパ球数減少6例（10.7%）であった。

〈キャッスルマン病〉

17.1.5 国内第Ⅱ相試験

(1) 第一段階

キャッスルマン病患者7例を対象として同一患者内での漸増法にて2、4、8mg/kg[注2)]と増量し（各用量ともに2週間隔にて3回反復投与）、各用量での有効性を検討した。その結果、CRP等の炎症マーカーは、2、4mg/kgでは各投与1週後で低下したものの2週後には再び上昇した症例もみられた。8mg/kgではほとんどの症例は投与期間を通じて低下傾向が持続した[26)]。

注2）キャッスルマン病の承認用量は、1回8mg/kgである。

(2) 第二段階

キャッスルマン病患者28例を対象として8mg/kgを2週間隔で8回反復投与した。その結果、炎症マーカー（CRP、フィブリノーゲン、ESR）、全身倦怠感（Visual Analog Scaleによる評価）、貧血状態（Hb）、低アルブミン血症等が、初回投与後より投与期間を通じて有意に改善した[26)]。

表3　有効性評価項目の推移（第二段階）

項　目	投与前	投与6週後	投与16週後
CRP（mg/dL）	8.7±5.0	1.2±1.7**	0.9±2.0**
フィブリノーゲン（mg/dL）	639±188	356±149**	317±138**
ESR（mm/hr）	114±34	63±36**	48±40**
全身倦怠感（0-100mm）	29.9±22.8	17.4±17.2*	17.7±16.5**
Hb（g/dL）	9.2±2.3	11.6±1.9**	12.0±2.1**
アルブミン（g/dL）	2.7±0.5	3.6±0.5**	3.7±0.5**

＊：p<0.05、＊＊：p<0.01、対応のある t検定（例数：24-28、平均値±SD）

(3) 継続投与試験

第一段階、第二段階において検討されたキャッスルマン病患者のうち33例を対象として、原則8mg/kgを2週間隔で長期継続投与（最長1568日、平均1191日）した結果、炎症マーカーをはじめとして治療効果が維持された。

なお、治療効果の維持が不十分であった7例では、投与間隔の短縮（最短1週間隔まで）により炎症マーカーの改善が認められた[27)]。

副作用発現頻度は、35例中33例（94.3%）であった。主な副作用は、鼻咽頭炎28例（80.0%）、発疹11例（31.4%）、瘙痒症10例（28.6%）、好中球数減少9例（25.7%）、口腔咽頭痛8例（22.9%）、下痢7例（20.0%）、背部痛7例（20.0%）、倦怠感7例（20.0%）、血中トロンビン異常7例（20.0%）、血中トリグリセリド増加7例（20.0%）であった。

〈成人スチル病〉

17.1.6 国内第Ⅲ相二重盲検比較試験

(1) 二重盲検期間（12週間）

副腎皮質ステロイドに対して効果不十分な成人発症スチル病患者26例を対象としてトシリズマブ8mg/kg又はプラセボを2週間隔で投与した。4週時のACR基準50%改善頻度はトシリズマブ投与群で61.5%（8/13例）、プラセボ群で30.8%（4/13例）であった（P＝0.238、Fisherの正確検定）。また、12週時のステロイド20%減量達成率（ACR基準50%改善かつ発熱が認められず、かつ副腎皮質ステロイドの投与量をベースラインから20%以上減量できた被験者の割合）はトシリズマブ投与群61.5%（8/13例）、プラセボ群23.1%（3/13例）であった[28)]。

(2) 非盲検期間（40週間）

二重盲検期間終了後、非盲検下で全例にトシリズマブ8mg/kgを原則2週間隔で投与した。非盲検期間終了時のステロイド5mg/日以下達成率（ACR基準50%改善かつ発熱が認められず、かつ副腎皮質ステロイドの投与量が5mg/日以下の被験者の割合）はトシリズマブ投与群で45.5%（5/11例）、プラセボからトシリズマブに切り替えた群で 81.8%（9/11例）であった。二重盲検期間開始時及び非盲検期間終了時の副腎皮質ステロイド投与量（平均値±標準偏差、例数）は、トシリズマブ群では23.0±16.2mg/日（13例）及び6.4±5.1mg/日（11例）、プラセボからトシリズマブに切り替えた群では32.5±20.4mg/日（13例）及び3.3±2.4mg/日（11例）であり、それぞれ減少した[28)]。

副作用発現頻度は、安全性解析対象症例27例中23例（85.2%）であった。主な副作用は、上気道感染13例（48.1%）、白癬5例（18.5%）、発疹3例（11.1%）、脂質異常症3例（11.1%）、胃腸炎3例（11.1%）、歯周病3例（11.1%）、肝機能異常3例（11.1%）等であった。

〈悪性腫瘍治療に伴うサイトカイン放出症候群〉

17.1.7 国際共同第Ⅱ相試験

3歳（スクリーニング時）～21歳（初診時）の再発又は難治性のB細胞性急性リンパ芽球性白血病患者に対して、チサゲンレクルユーセルを投与する非盲検非対照試験を実施した。チサゲンレクルユーセルの輸注を受けた75例のうち、重症度が高いサイトカイン放出症候群（CRS）を発症した28例（日本人1例）に、体重30kg未満の患者にはトシリズマブ12mg/kg、体重30kg以上の患者にはトシリズマブ8mg/kg（最大800mgまで）を単剤又は副腎皮質ステロイド等との併用で投与し、症状の改善が認められない場合は、最大3回まで反復投与した。その結果、トシリズマブが投与された28例全例（100.0%）が回復した。トシリズマブ投与からCRS回復判断時点までの期間の中央値［95%信頼区間（CI）］は、5.0（4.0、7.0）日（最小値～最大値：2～29日）であった。CRSの回復は、24時間以上平熱が持続し、昇圧薬服用の必要がないと判断した期間が24時間以上持続した時点と定義した。

28例におけるトシリズマブ投与日以降に認められた主な有害事象は、CRS[#3]22例（78.6%）、発熱、AST増加、好中球数減少、低カリウム血症各8例（28.6%）、ALT増加、急性腎障害、低酸素症、高血圧各7例（25.0%）、貧血、腹痛、嘔吐、血中ビリルビン増加、白血球数減少、高血糖、低カルシウム血症、頭痛、低血圧各6例（21.4%）等であった[29)]。

17.1.8 国際共同第Ⅱ相試験

18歳以上の再発又は難治性のびまん性大細胞型B細胞リンパ腫成人患者に対して、チサゲンレクルユーセルを投与する非盲検非対照試験を実施した。チサゲンレクルユーセルの輸注を受けた111例のうち、重症度が高いCRSを発症した16例にトシリズマブ8mg/kg（最大800mgまで）[#4]を単剤又は副腎皮質ステロイド等との併用で投与し、症状の改善が認められない場合は、最大2回まで反復投与した。その結果、トシリズマブが投与された16例のうち、15例（93.8%）が回復、1例が疾患進行による死亡のための評価打ち切りであった。トシリズマブ投与からCRS回復判断時点までの期間の中央値（95%CI）は、6.0（3.0、7.0）日（最小値～最大値：2～14日）であった。

16例におけるトシリズマブ投与日以降に認められた主な有害事象は、CRS[#3]、低血圧各9例（56.3%）、血小板数減少8例（50.0%）、急性腎障害、貧血各6例（37.5%）、下痢、白血球数減少各5例（31.3%）、血中クレアチニン増加、高血糖、低リン酸血症、全身性浮腫、末梢性浮腫、血中フィブリノゲン減少、好中球数減少各4例（25.0%）等であった[29)]。

#3：有害事象のCRSは、再発又は難治性のB細胞性急性リンパ芽球性白血病の国際共同第Ⅱ相試験の1例を除き、トシリズマブ初回投与日前に発現したCRSが継続している中で重症度の変化により有害事象として報告された事象及びトシリズマブ初回投与日のトシリズマブ投与前に発現した事象であった。

#4：トシリズマブの用量について、体重30kg以上は1回8mg/kg、体重30kg未満は1回12mg/kgを投与することと規定されていたが、試験に組み入れられた患者はいずれも体重30kg以上の患者であり、1回8mg/kgが投与された。

＊＊17.1.9 国内第Ⅰ/Ⅱ相試験

再発又は難治性のB細胞性非ホジキンリンパ腫患者に対して、エプコリタマブ（遺伝子組換え）を投与する非盲検非対照試験を実施した。用量漸増パート又は用量拡大パートにおいてエプコリタマブの投与を受けた66例中、CRSは57例に発現し、うち18例にトシリズマブ[#5]を投与（副腎皮質ステロイド等との併用も可）した。その結果、トシリズマブが投与された有効性解析対象の15例全例

（100.0%）が回復した。トシリズマブ投与からCRS[#6]回復判断時点までの期間の中央値（95%CI）は、2.0（2.0、3.0）日（最小値～最大値：1.0～7.0日）であった。

トシリズマブの投与回数の内訳は、1回が10例（66.7%）、2回が3例（20.0%）、4回以上が2例（13.3%）であった。

安全性解析対象症例15例におけるトシリズマブ投与日以降に認められた主な有害事象は、CRS12例（80.0%）[#7]、好中球数減少6例（40.0%）、AST増加4例（26.7%）、リンパ球数減少4例（26.7%）、低カリウム血症4例（26.7%）、注射部位紅斑3例（20.0%）、ALT増加3例（20.0%）、血小板数減少3例（20.0%）、白血球数減少3例（20.0%）等であった[30]。

#5：トシリズマブの用法・用量について、①CRS管理ガイダンス（Biol Blood Marrow Transplant 2019;25:625-38）（1回8mg/kg（最大800mg）、8時間以上経過後にトシリズマブを適宜再投与する（24時間で最大2回まで））及び②腫瘍特異的T細胞輸注療法に伴うCRSに係る承認された用法・用量（体重30kg未満の患者には1回12mg/kg、体重30kg以上の患者には1回8mg/kgを投与）を参考に決定され、実際の投与量は7.3～8.5mg/kgであった。

#6：トシリズマブ投与に至った初回のCRS

#7：トシリズマブ初回投与日のトシリズマブ投与前に認められた事象及びトシリズマブの投与を行ったCRSが回復した後の次回以降のエプコリタマブの投与後に認められた事象を除くと、CRSが発現した症例は2例であった。

〈SARS-CoV-2による肺炎〉

17.1.10 国内試験

18歳以上のSARS-CoV-2による肺炎患者を対象として標準治療併用下においてトシリズマブ8mg/kg（最大800mgまで）を最大2回投与する（初回投与後8-24時間後に症状の悪化又は改善が認められない場合に1回追加投与可能）国内単群試験を実施した。本試験の主な選択・除外基準は表4のとおりであった。

表4　主な選択・除外基準

選択基準	・いずれかの検体（呼吸器、血液、尿、便、その他の体液等）でPCR陽性が確認され、胸部X線又はCTスキャンにより確認されたSARS-CoV-2による肺炎で入院した患者 ・SpO_2が93%以下又はPaO_2/FiO_2が300mmHg未満
除外基準	・AST又はALTが基準値上限の10倍超 ・好中球数が1,000/μL未満 ・血小板数が50,000/μL未満 ・妊婦又は授乳婦

主要評価項目であった投与開始28日時点の7カテゴリ順序尺度[#8]を用いて評価した臨床状態の結果は表5のとおりであった。

表5　7カテゴリ順序尺度を用いて評価した臨床状態

7カテゴリ順序尺度	48例	
	ベースライン（1日目）	28日目
1	0	35（72.9）
2	4（8.3）	3（6.3）
3	29（60.4）	2（4.2）
4	8（16.7）	0
5	6（12.5）	3（6.3）
6	1（2.1）	0
7	0	5（10.4）

例数（%）

副作用発現頻度は、安全性解析対象症例48例中15例（31.3%）であった。主な副作用は、AST増加6例（12.5%）、ALT増加6例（12.5%）等であった[31]。

#8：7カテゴリ順序尺度（1：退院又は退院待機状態、2：ICU以外の病棟に入院中で酸素投与が不要、3：ICU以外の病棟に入院中で酸素投与が必要、4：ICU又はICU以外の病棟に入院中で非侵襲的換気又は高流量酸素が必要、5：ICUに入院中で挿管及び人工呼吸器が必要、6：ICUに入院中でECMOが必要あるいは人工呼吸器及び臓器補助の追加が必要、7：死亡）

18．薬効薬理

18.1 作用機序

本薬は*in vitro*において、可溶性及び膜結合性 IL-6レセプターに結合してそれらを介したIL-6の生物活性の発現を抑制した[32]。また、本薬は、カニクイザルに投与されたヒトIL-6の活性発現を抑制した[33]。

18.2 関節炎抑制・改善作用

本薬は、カニクイザルコラーゲン誘発関節炎において、関節炎発症前からの投与により関節腫脹の発現を抑制するとともに、関節炎発症後の投与により関節の腫脹を改善した[34),35]。

18.3 IL-6トランスジェニックマウスでの病態発現抑制作用

抗マウスIL-6レセプター抗体は、IL-6トランスジェニックマウスでの貧血状態、蛋白尿、高γグロブリン血症等の所見の発現を抑制し、生存日数を延長させた[36]。

19．有効成分に関する理化学的知見

一般的名称：トシリズマブ（遺伝子組換え）
（Tocilizumab（Genetical Recombination））（JAN）

分子式：軽鎖（$C_{1033}H_{1606}N_{278}O_{337}S_6$）
重鎖（$C_{2181}H_{3398}N_{582}O_{672}S_{15}$：主成分）

分子量：約148,000

構造式：アミノ酸214個の軽鎖2分子とアミノ酸447、448（主成分）又は449個の重鎖2分子からなる糖蛋白質

20．取扱い上の注意

外箱開封後は遮光して保存すること。

21．承認条件

21.1 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

〈アクテムラ点滴静注用80mg〉
4mL×1バイアル

〈アクテムラ点滴静注用200mg〉
10mL×1バイアル

〈アクテムラ点滴静注用400mg〉
20mL×1バイアル

＊＊23．主要文献

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16）社内資料：全身型若年性特発性関節炎患者に対する臨床薬理
17）社内資料：キャッスルマン病患者を対象とした第Ⅱ相試験での薬物動態
18）社内資料：成人発症スチル病患者での血清中トシリズマブ濃度推移
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（MRA006JP試験）
28）社内資料：成人発症スチル病患者に対する第Ⅲ相試験（医師主導）
29）社内資料：国際共同第Ⅱ相試験（チサゲンレクルユーセル）
30）社内資料：国内第Ⅰ/Ⅱ相試験（エプコリタマブ）
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24．文献請求先及び問い合わせ先

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26．製造販売業者等

26.1 製造販売元

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NOVARTIS

1. 警告

1.1 本剤投与により、敗血症を含む重篤な感染症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回ると判断される場合にのみ本剤を投与すること。また、本剤の投与において、重篤な感染症等の副作用により、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、速やかに担当医に連絡するよう患者に注意を与えること。[1.2、2.1、8.1、8.2、8.6、9.1.1、9.1.3、9.1.4、11.1.1参照]

1.2 敗血症等の致命的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現に注意すること。[1.1、2.1、8.1、8.2、9.1.1、9.1.3、9.1.4、11.1.1参照]

1.3 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［感染症が悪化するおそれがある。］［1.1、1.2、8.1、8.2、9.1.1、9.1.3、9.1.4、11.1.1参照］

2.2 活動性結核の患者［症状が悪化するおそれがある。］［8.3、9.1.2参照］

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	イラリス皮下注射液150mg	
有効成分	1mL中[注1)] カナキヌマブ（遺伝子組換え）150.0mg	
添加剤	1mL中[注1)]	
	D-マンニトール	49.2mg
	L-ヒスチジン	2.1mg
	L-ヒスチジン塩酸塩水和物	1.3mg
	ポリソルベート80	0.4mg

本剤の有効成分であるカナキヌマブ（遺伝子組換え）は、マウスハイブリドーマ細胞Sp2/0-Ag14から産生されるヒト型モノクローナル抗体である。本剤は、製造工程において、ヒト血清アルブミン、ヒト血清トランスフェリン及びブタトリプシン（膵臓由来）を使用している。

注1）注射液吸引時の損失を考慮し、1バイアルから1mLを注射するに足る量を確保するため過量充填されている。

3.2 製剤の性状

販売名	イラリス皮下注射液150mg
性状	無色～微黄褐色の澄明又は混濁した液
pH	6.2～6.8
浸透圧	350～450mOsm/kg

4. 効能又は効果

○以下のクリオピリン関連周期性症候群
- 家族性寒冷自己炎症症候群
- マックル・ウェルズ症候群
- 新生児期発症多臓器系炎症性疾患

○高IgD症候群（メバロン酸キナーゼ欠損症）
○TNF受容体関連周期性症候群
既存治療で効果不十分な下記疾患
○家族性地中海熱
○全身型若年性特発性関節炎
○成人発症スチル病

5. 効能又は効果に関連する注意

〈家族性地中海熱〉

5.1 コルヒチン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。

〈全身型若年性特発性関節炎及び成人発症スチル病〉

5.2 副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。

5.3 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MASを合併している患者ではMASに対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中にMASが発現した場合は、休薬を考慮し、速やかにMASに対する適切な治療を行うこと。

6. 用法及び用量

〈クリオピリン関連周期性症候群〉

通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを8週毎に皮下投与する。

十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが、1回最高用量は体重40kg以下の患者では8mg/kg、体重40kgを超える患者では600mgとする。

最高用量まで増量し、8週以内に再燃がみられた場合には、投与間隔を4週間まで短縮できる。

なお、症状に応じて1回投与量の増減を検討すること。

〈高IgD症候群（メバロン酸キナーゼ欠損症）〉

通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを、4週毎に皮下投与する。

十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1回最高用量は体重40kg以下の患者では6mg/kg、体重40kgを超える患者では450mgとする。

〈TNF受容体関連周期性症候群及び家族性地中海熱〉

通常、体重40kg以下の患者にはカナキヌマブ（遺伝子組換え）として1回2mg/kgを、体重40kgを超える患者には1回150mgを、4週毎に皮下投与する。

十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1回最高用量は体重40kg以下の患者では4mg/kg、体重40kgを超える患者では300mgとする。

〈全身型若年性特発性関節炎及び成人発症スチル病〉

通常、カナキヌマブ（遺伝子組換え）として1回4mg/kgを、4週毎に皮下投与する。1回最高用量は300mgとする。

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7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤の至適用量は患者の体重及び臨床症状によって異なり、投与量は患者毎に設定する必要がある。

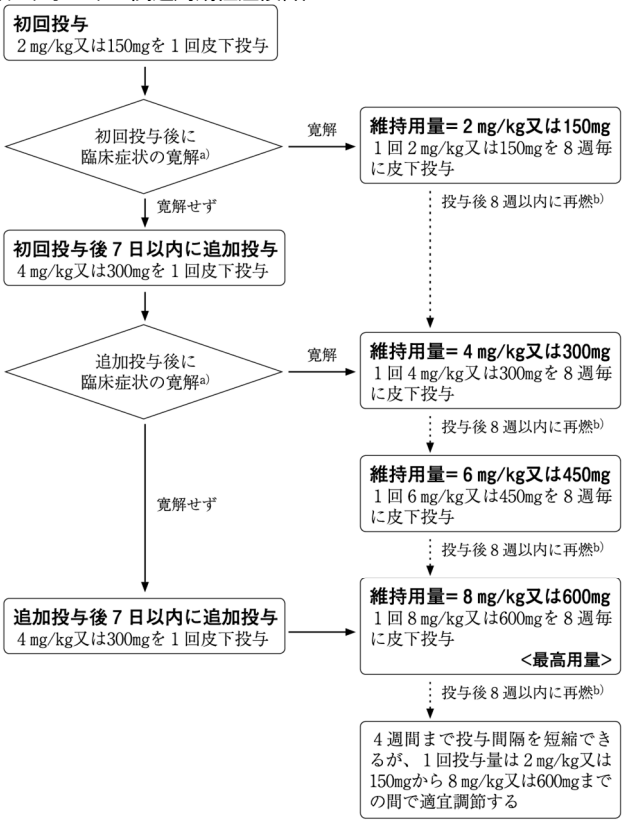
7.2 本剤と他の生物製剤の併用について安全性及び有効性は確立していないので併用を避けること。

〈クリオピリン関連周期性症候群、高 IgD 症候群（メバロン酸キナーゼ欠損症）、TNF 受容体関連周期性症候群、家族性地中海熱〉

7.3 投与は1回2mg/kg又は150mgの低用量から開始し、十分な効果がみられない、もしくは再燃がみられた場合に限り、下図を参考に投与量の増量を行うこと。[17.1.1、17.1.5参照]

十分な臨床的効果がみられない場合の漸増方法

〈クリオピリン関連周期性症候群〉

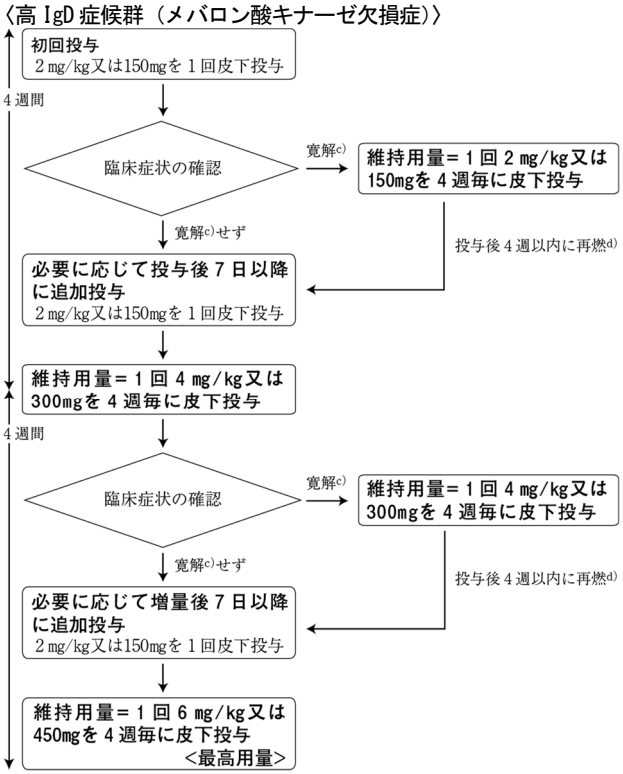


a）国内臨床試験における寛解の基準（以下の1～3をすべて満たす場合）
＜臨床的寛解＞
1．医師による自己炎症性疾患活動性の総合評価注2) が軽微以下
2．皮膚疾患の評価注2) が軽微以下
＜血清学的寛解＞
3．CRPが10mg/L（＝1 mg/dL）未満又はSAAが10mg/L（=10μg/mL）未満

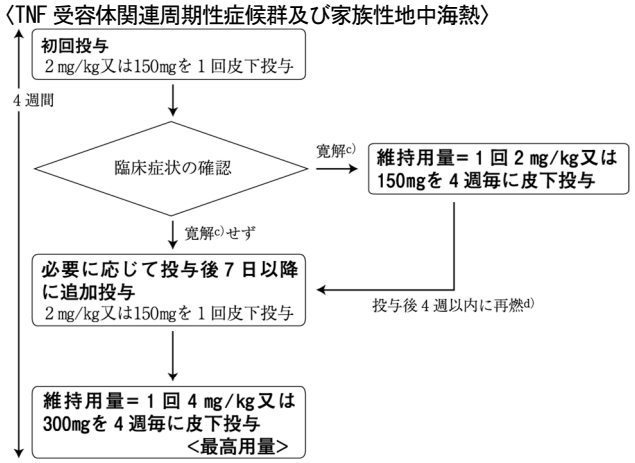
b）国内臨床試験における再燃の基準（以下の1～2をすべて満たす場合）
＜臨床的再燃＞
1．医師による自己炎症性疾患活動性の総合評価注2) が軽度以上、又は医師による自己炎症性疾患活動性の総合評価注2) が軽微かつ皮膚疾患の評価注2) が軽度以上
＜血清学的再燃＞
2．CRPが30mg/L（＝3 mg/dL）超又はSAAが30mg/L（=30μg/mL）超

注2）評価基準：なし、軽微、軽度、中等度、重度の5段階

〈高 IgD 症候群（メバロン酸キナーゼ欠損症）〉



〈TNF 受容体関連周期性症候群及び家族性地中海熱〉



c）臨床試験における寛解の基準（以下の1～2をすべて満たす場合）
＜臨床的寛解＞
1．医師による自己炎症性疾患活動性の総合評価注3) が軽微以下
＜血清学的寛解＞
2．CRPが10mg/L以下又はベースラインと比べ70%以上の減少

d）臨床試験における再燃の基準（以下の1～2をすべて満たす場合）
＜臨床的再燃＞
1．医師による自己炎症性疾患活動性の総合評価注3) が軽度以上
＜血清学的再燃＞
2．CRPが30mg/L（＝3 mg/dL）以上

注3）評価基準：なし、軽微、軽度、中等度、重度の5段階

8. 重要な基本的注意

8.1 臨床試験において、上気道感染等の感染症が高頻度に報告されており、重篤な感染症も報告されているため、本剤投与中は感染症の発現、再発及び増悪に十分注意すること。[1.1、1.2、2.1、9.1.1、9.1.3、9.1.4、11.1.1参照]

8.2 本剤により感染に対する炎症反応が抑制される可能性があるため、本剤投与中は患者の状態を十分に観察すること。[1.1、1.2、2.1、9.1.1、9.1.3、9.1.4、11.1.1参照]

8.3 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（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。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の発現には十分に注意し、患者に対し、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説明すること。なお、結核の活動性が確認された場合は結核の治療を優先し、本剤を投与しないこと。[2.2、9.1.2参照]

8.4 本剤投与により好中球減少があらわれることがあるので、初回投与前、概ね投与1ヵ月後、及びその後本剤投与中は定期的に好中球数を測定すること。[11.1.2参照]

8.5 臨床試験において、アナフィラキシー又はアナフィラキシーショックは報告されていないが、本剤の投与に対する過敏症反応が報告されているため、重篤な過敏症反応のリスクを除外することはできない。本剤を投与する際には過敏症反応の発現に注意し、必要に応じて適切な処置を行うこと。

8.6 本剤を投与された患者において、悪性腫瘍が報告されている。本剤を含む抗IL-1製剤との関連性は明らかではないが、悪性腫瘍等の発現には注意すること。[1.1参照]

8.7 本剤投与中は、生ワクチン接種による感染症発現のリスクを否定できないため、生ワクチン接種は行わないこと。本剤投与前に、必要なワクチンを接種しておくことが望ましい。

8.8 抗リウマチ生物製剤による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。[9.1.5参照]

8.9 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。

8.10 本剤は、マスターセルバンク作製時において、培地成分の一部としてヒト血清アルブミン及びヒト血清トランスフェリンを使用しているが、最終製品の成分としては含まれていない。これらヒト血液由来成分のうち、ヒト血清アルブミンの原血漿に対してC型肝炎ウイルス（HCV）に対する核酸増幅検査を実施している。原血漿を対象としたその他の核酸増幅検査は実施していないが、血清学的検査によりウイルスの抗原又はウイルスに対する抗体が陰性であることを確認している。更に、これらヒト血液由来成分及びカナキヌマブ（遺伝子組換え）の製造において、複数の工程によりウイルスの除去・不活化をしており、最終製品へのB型肝炎ウイルス（HBV）、C型肝炎ウイルス（HCV）及びヒト免疫不全ウイルス（HIV-1及びHIV-2）混入の可能性は極めて低い。また、ヒト血清アルブミンの製造にオランダで採血したヒト血液を用いているが、本剤の投与により伝達性海綿状脳症（TSE）がヒトに伝播したとの報告はなく、TSEに関する理論的なリスク評価値は、一定の安全性を確保する目安に達しており、本剤によるTSE伝播のリスクは極めて低い。本剤の投与に際しては、その旨の患者又はその保護者への説明を考慮すること。

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

感染症が悪化するおそれがある。[1.1、1.2、2.1、8.1、8.2、11.1.1参照]

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

結核の診療経験がある医師に相談すること。結核を活動化させるおそれがある。以下のいずれかの患者には、原則として抗結核薬を投与した上で、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

[2.2、8.3参照]

9.1.3 再発性感染症の既往歴のある患者

感染症が再発するおそれがある。[1.1、1.2、2.1、8.1、8.2、11.1.1参照]

9.1.4 易感染性の状態にある患者

感染症を誘発するおそれがある。[1.1、1.2、2.1、8.1、8.2、11.1.1参照]

9.1.5 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抗体又はHBs抗体陽性）

最新のB型肝炎治療ガイドラインを参考に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。[8.8参照]

9.5 妊婦

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。動物実験（マーモセット）で胎児への移行が認められている。

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。動物実験（マウス）でマウス抗マウスIL-1β抗体を母動物に授乳期まで投与した際、マウス新生児に同抗体が移行したとの報告がある。

9.7 小児等

低出生体重児、新生児、乳児又は2歳未満の幼児に対する安全性及び有効性を検討することを目的とした臨床試験は実施していない。

9.8 高齢者

一般に生理機能が低下しているので注意すること。

10. 相互作用

本剤と他の薬剤との相互作用を検討した臨床試験は実施されていない。

代謝酵素チトクロームP450（CYP450）の発現は、IL-1β等の炎症性サイトカインにより抑制されているとの報告があり、本剤のIL-1β阻害作用により、CYP450の発現が増加する可能性がある。CYP450により代謝され、治療域が狭い薬剤と併用する場合には、これらの薬剤の効果や血中濃度に関するモニタリングを行い、必要に応じて投与量を調節すること。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
抗TNF製剤	重篤な感染症発現のリスクが増大するおそれがある。また、他の抗IL-1製剤と抗TNF製剤との併用により、重篤な感染症の発現頻度増加が認められているため、本剤との併用は行わないことが望ましい。	共に免疫抑制作用を有するため。

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 重篤な感染症（~~10.2~~12.7%）

敗血症や日和見感染症（アスペルギルス症、非定型抗酸菌症、帯状疱疹等）等の重篤な感染症があらわれることがある。[1.1、1.2、2.1、8.1、8.2、9.1.1、9.1.3、9.1.4参照]

11.1.2 好中球減少（頻度不明）

[8.4参照]

11.2 その他の副作用

	5%以上	5%未満	頻度不明
感染症	鼻咽頭炎	胃腸炎、肺炎、副鼻腔炎、上気道感染、咽頭炎、尿路感染	~~尿路感染、~~気管支炎、ウイルス感染、扁桃炎、鼻炎、耳感染、外陰部膣カンジダ症、下気道感染、肺感染
神経系	－	頭痛	回転性めまい
過敏症	~~－~~過敏症反応	－	~~過敏症反応~~
皮膚	注射部位反応	－	－
消化器	－	口内炎、下痢	~~下痢、~~腹痛
肝臓	－	AST・ALT上昇	－
血液	－	白血球数減少	血小板数減少
その他	－	－	体重増加

14. 適用上の注意

14.1 薬剤調製時の注意

14.1.1 投与前の準備

(1) 巻末の投与液量一覧表を参考に、必要数のバイアル、投与用注射筒（必要液量を正確に採取できる注射筒）及び注射針（21ゲージ及び27ゲージ）を用意すること。

(2) 投与前に冷蔵庫から取り出し室温に戻しておくこと。また、バイアルを振ったり、上下を逆にしないこと。

14.2 薬剤投与時の注意

14.2.1 溶液内に粒子がある場合等、外観に異常を認めた場合には使用しないこと。

14.2.2 バイアルのゴム栓部分をアルコール綿等で消毒する。

14.2.3 投与量に応じて必要な液量を、21 ゲージの注射針を装着した注射筒を用いて注意深く採取する。このとき、必要液量を正確に採取できる注射筒を用いること。

14.2.4 採取後、27 ゲージの注射針を用いて皮下投与する。

14.2.5 瘢痕組織への投与を避けること。

14.2.6 1 回につき 1.0mL を超えて投与する場合には、1 箇所あたり 1.0mL を超えないように部位を分けて投与すること。

14.2.7 1 バイアルは 1 回のみの使用とし、使用後の残液は微生物汚染のおそれがあるので、再使用しないこと。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 クリオピリン関連周期性症候群患者を対象とした国内及び海外臨床試験において、白血球数及び血小板数の平均値が減少したが、これらの変動は炎症反応の低下による可能性がある。

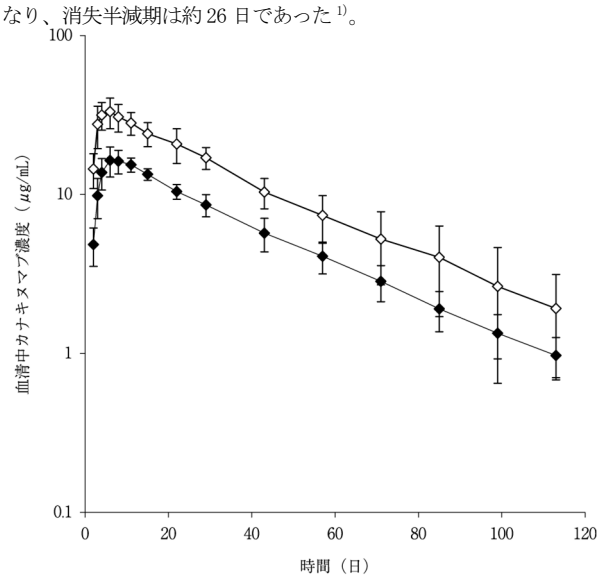
15.1.2 クリオピリン関連周期性症候群患者を対象とした海外臨床試験において、トランスアミナーゼ上昇を伴わない、無症候性で軽度の血清ビリルビン上昇が報告されている。

16. 薬物動態

16.1 血中濃度

16.1.1 健康成人での成績

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg 又は 300mg を皮下投与したとき、血清中カナキヌマブ濃度は投与後 5 日目に最高となり、消失半減期は約 26 日であった[1)]。



◆：150mg、◇：300mg（平均値±標準偏差）

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg 又は 300mg を単回皮下投与したときの血清中濃度推移（n=6）

日本人健康成人男子にカナキヌマブ（遺伝子組換え）150mg 又は 300mg を単回皮下投与したときの薬物動態パラメータ（n=6）

	150mg	300mg
Cmax（μg/mL）	16.9±2.62	34.1±6.09
Tmax（day）	5［5～10］	5［2～5］
$AUC_{0\text{-}inf}$（μg・day/mL）	663±79.6	1,300±275
$T_{1/2}$（day）	26.3±2.02	26.9±8.23
CL/F（L/day）	0.229±0.0319	0.238±0.0421
Vz/F（L）	8.70±1.34	8.92±1.64

平均値±標準偏差、Tmax に関しては中央値［最小～最大］

日本人健康成人男子にカナキヌマブ（遺伝子組換え）を静脈内投与したときのクリアランス（CL）は 0.160～0.174L/day、定常状態における分布容積（Vss）は 5.44～5.77L であった。カナキヌマブ（遺伝子組換え）150mg～300mg の皮下投与時又は 0.30～10.0mg/kg の静脈内投与時、AUC 及び Cmax は用量に比例して増加した[1)]（本剤の承認された投与経路は皮下投与であり、1 回最高用量は 600mg である）。

16.1.2 患者での成績

〈クリオピリン関連周期性症候群患者〉

母集団薬物動態-薬力学解析よりベイズ推定した D2308 試験の日本人クリオピリン関連周期性症候群患者（平均体重：28.8kg）の CL 及び Vss の平均値±標準偏差は 0.0915±0.048L/day 及び 2.45±1.15L であった。

外国人成人クリオピリン関連周期性症候群患者にカナキヌマブ（遺伝子組換え）150mg を皮下投与したとき、血清中カナキヌマブ濃度は投与後約 7 日目に最高となり、消失半減期は約 26 日であった。また、皮下投与時のバイオアベイラビリティは約 67%であった。4～17 歳の外国人クリオピリン関連周期性症候群患者にカナキヌマブ（遺伝子組換え）2mg/kg 又は 150mg を皮下投与したとき、血清中カナキヌマブ濃度は投与後 2～7 日目に最高となり、薬物動態パラメータの値は 18 歳以上の外国人で認められている値と同程度であった[2)]。

母集団薬物動態-薬力学解析の結果、カナキヌマブ（遺伝子組換え）のクリアランス及び分布容積は体重に依存することが示された。

〈クリオピリン関連周期性症候群患者、高 IgD 症候群（メバロン酸キナーゼ欠損症）患者、TNF 受容体関連周期性症候群患者、家族性地中海熱患者〉

日本人及び外国人のクリオピリン関連周期性症候群患者、高 IgD 症候群（メバロン酸キナーゼ欠損症）患者、TNF 受容体関連周期性症候群患者、家族性地中海熱患者から得られた血清中カナキヌマブ濃度を用いて母集団薬物動態解析を実施した。カナキヌマブ（遺伝子組換え）のクリアランス及び分布容積は体重に依存することが示された。平均体重（55kg）での CL 及び Vss の母集団平均値はそれぞれ 0.14L/day 及び 4.96L であった。日本人と外国人でカナキヌマブ（遺伝子組換え）の薬物動態は同様であった[3)]。

〈全身型若年性特発性関節炎患者〉

日本人及び外国人の全身型若年性特発性関節炎患者から得られた血清中カナキヌマブ濃度を用いて母集団薬物動態解析を実施した。カナキヌマブ（遺伝子組換え）のクリアランス及び分布容積は体重に依存することが示された。日本人全身型若年性特発性関節炎患者（体重 33kg）の CL 及び Vss の母集団平均値は 0.079L/day 及び 2.95L であった。日本人と外国人でカナキヌマブ（遺伝子組換え）の薬物動態は同様であった[4)]。

〈成人発症スチル病患者〉

全身型若年性特発性関節炎患者の母集団薬物動態モデルを用いて、日本人及び外国人の成人発症スチル病患者から得られた血清中カナキヌマブ濃度から薬物動態パラメータのシミュレーションを行った。日本人成人発症スチル病患者（平均体重 57.2kg）の CL 及び Vss の母集団薬物動態モデルからの推定値の平均値は 0.201L/day 及び 6.16L であった。日本人と外国人でカナキヌマブ（遺伝子組換え）の薬物動態は同様であった。また、全身型若年性特発性関節炎患者及び成人発症スチル病患者の薬物動態は同様であった[5)]。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈クリオピリン関連周期性症候群（家族性寒冷自己炎症症候群、マックル・ウェルズ 症候群、新生児期発症多臓器系炎症性疾患）〉

17.1.1 国内第Ⅲ相試験

クリオピリン関連周期性症候群（マックル・ウェルズ症候群又は新生児期発症多臓器系炎症性疾患）患者 19 例（2～14 歳の患者 11 例を含む）を対象とした非盲検、非対照試験（D2308 試験）で、体重 40kg 以下の患者には本剤 1 回 2mg/kg、体重 40kg を超える患者には本剤 1 回 150mg を皮下投与し、寛解が得られない場合又は投与後 8 週以内に再燃がみられた場合は本剤 1 回 2mg/kg 又は 150mg ずつ増量して投与した。ただし、1 回最高用量は本剤 8mg/kg 又は 600mg とした。その結果、投与 24 週以内及び投与 48 週以内に寛解した患者の割合はそれぞれ 94.7%（18/19 例）及び 100%（19/19 例）、寛解した患者のうち投与 24 週後及び投与 48 週後の時点で再燃がみられなかった患者の割合はそれぞれ 77.8%（14/18 例）及び 84.2%（16/19 例）であった。また、初回投与後 14 日以内に炎症マーカーである CRP 及び血清アミロイド A 蛋白（SAA）の低下がみられた[5,6)]。

副作用は 19 例中 12 例（63.2%）に認められた。主な副作用は鼻咽頭炎（3 例、15.8%）、蕁麻疹、口内炎（各 2 例、10.5%）であった。[7.3 参照]

17.1.2 外国第Ⅱ相試験

NALP3（NLRP3）変異を有するクリオピリン関連周期性症候群患者 34 例（4～17 歳の患者 7 例を含む）を対象とした非盲検、非対照試験（A2102 試験）で、初回投与時及び再燃時に 16 歳未満の患者（5 例）には本剤 1 回 2mg/kg、16 歳以上の患者には本剤 1 回 150mg を皮下投与した。その結果、16 歳未満の患者では初回投与後 2～8 日以内に 5 例全例、16 歳以上の患者では初回投与後 2～9 日以内に 96.6%（28/29 例）の患者が寛解した。また、初回投与後 1 週間以内に CRP 及び SAA の低下がみられた[2)]。

副作用は 34 例中 13 例（38.2%）に認められた。主な副作用は回転性めまい、多汗症、発疹（各 2 例、5.9%）であった。

17.1.3 外国第Ⅲ相試験

マックル・ウェルズ症候群患者 35 例を対象とした D2304 試験で、全例に初回用量として体重 15～40kg の患者には本剤 1 回 2mg/kg、体重 40kg を超える患者には本剤 1 回 150mg を皮下投与した（非盲検期）。この初回投与で寛解した患者に対して、8 週後以降は体重 15～40kg の患者には本剤 1 回 2mg/kg 又はプラセボ、体重 40kg を超える患者には本剤 1 回 150mg 又はプラセボを 8 週毎に再燃がみられるまで投与し（二重盲検期：最大 24 週間）、再燃後又は 24 週経過後は全例に体重 15～40kg の患者には本剤 1 回 2mg/kg、体重 40kg を超える患者には本剤 1 回 150mg を 8 週毎に投与した（非盲検期）。その結果、初回投与後 8 週以内に 97.1%（34/35 例）の患者が寛解した。二重盲検期の 24 週以内に本剤投与群全例（15 例）で再燃がみられなかったのに対し、プラセボ投与群では 81.3%（13/16 例）で再燃がみられた。24 週後以降も投与を継続した 31 例中、再燃がみられたのは 1 例であった。また、初回投与後 8 日以内に CRP 及び SAA の低下がみられた[6,7)]。

非盲検期（0～8 週）の副作用は 35 例中 12 例（34.3%）に認められた。主な副作用は体重増加（3 例、8.6%）、無力症、気管支炎（各 2 例、5.7%）であった。

二重盲検期（8～32 週）の副作用は本剤群で 15 例中 7 例（46.7%）に認められた。主な副作用は鼻咽頭炎、尿路感染（各 2 例、13.3%）であった。

非盲検期（32 週以降）の副作用は 31 例中 9 例（29.0%）に認められた。主な副作用は下痢（2 例、6.5%）であった。

17.1.4 外国第Ⅲ相試験

本剤による治療未経験のクリオピリン関連周期性症候群患者 109 例（3～17 歳の患者 38 例を含む）、A2102 及び D2304 試験からの移行例 57 例（5～17 歳の患者 9 例を含む）、計 166 例を対象とした非盲検、非対照試験（D2306 試験）を実施した。治療未経験例には初回用量として体重 40kg 以下の患者には本剤 1 回 2mg/kg、体重 40kg を超える患者には本剤 1 回 150mg を 8 週毎に皮下投与し、再燃がみられた場合には 1 回最高用量として本剤 8mg/kg 又は 600mg まで漸増し、6 ヵ月～最長 2 年間投与した。その結果、試験全体では投与終了時までに再燃が一度もみられなかった患者の割合は 76.5%（127/166 例）であった。また、治療未経験例では 78.0%（85/109 例）の患者が初回投与後 21 日以内に寛解した[7,8)]。

副作用は 166 例中 52 例（31.3%）に認められた。主な副作用は頭痛（6 例、3.6%）、回転性めまい、口唇乾燥、妊娠時の薬物曝露、体重増加、皮膚乾燥（各 3 例、1.8%）であった。

〈高 IgD 症候群（メバロン酸キナーゼ欠損症）、TNF 受容体関連周期性症候群、家族性地中海熱〉

17.1.5 国際共同第Ⅲ相試験

高 IgD 症候群患者（HIDS）／メバロン酸キナーゼ欠損症患者（MKD）72 例（日本人 1 例を含む）、TNF 受容体関連周期性症候群患者（TRAPS）46 例（日本人 6 例を含む）、コルヒチン効果不十分又は不耐容な家族性地中海熱患者（crFMF）63 例（日本人 1 例を含む）を対象とした N2301 試験で、体重 40kg 以下の患者には本剤 1 回 2mg/kg 又はプラセボ、体重 40kg を超える患者には本剤 1 回 150mg 又はプラセボを 4 週毎に再燃がみられるまで投与し（二重盲検期：最大 16 週間）、寛解が得られない場合は本剤 1 回 2mg/kg 又は 150mg ずつ増量して投与した。ただし、1 回最高用量は本剤 4mg/kg 又は 300mg とした。16 週後に寛解が得られた患者の割合（投与 14 日後に index flare の寛解[a)]が得られ、かつ 16 週間の投与中に新たな再燃[b)]が認められなかった患者の割合）を次表に示す。本剤投与群における 16 週後に寛解が得られた患者の割合は、いずれの疾患群でもプラセボ群に比べて有意に高かった。また、いずれの疾患群でも初回投与後 14 日以内に炎症マーカーである CRP 及び血清アミロイド A 蛋白（SAA）の低下がみられた[8,9)]。

疾患	本剤群	プラセボ群	プラセボ群との差 [95%CI]#、p 値##
HIDS/MKD	35（13/37）	6（2/35）	29［6, 50］ p=0.0020
TRAPS	45（10/22）	8（2/24）	37［8, 61］ p=0.0050
crFMF	61（19/31）	6（2/32）	55［31, 73］ p<0.0001

% （例数）
# 正確な信頼区間
Fisher’s exact 検定

a）Index flare の寛解：ランダム化時に認められた最初の再燃を index flare とし、投与 14 日後に以下の 2 つの条件を満たした場合、index flare の寛解とした。
- 臨床的寛解：医師による全般評価が軽微以下
- 血清学的寛解：CRP が正常範囲内（10 mg/L 以下）又はベースラインと比べ 70%以上の減少

b）新たな再燃：臨床的再燃と血清学的再燃が同時に認められた場合と定義した。
- 臨床的再燃：医師による全般評価が軽度以上
- 血清学的再燃：CRP 30 mg/L 以上

HIDS では、二重盲検期の副作用は本剤を投与された 68 例中 21 例（30.9%）に認められた。主な副作用は注射部位反応（4 例、5.9%）、下痢及び外陰部腟カンジダ症（各 3 例、4.4%）、上腹部痛、発熱、中耳炎、頭痛（各 2 例、2.9%）であった。

TRAPS では、二重盲検期の副作用は本剤を投与された 43 例中 14 例（32.6%）に認められた。主な副作用は注射部位反応（4 例、9.3%）、鼻咽頭炎（3 例、7.0%）であった。

crFMF では、二重盲検期の副作用は本剤を投与された 58 例中 19 例（32.8%）に認められた。主な副作用は注射部位反応（6 例、10.3%）、上気道感染、頭痛（各 3 例、5.2%）であった。[7.3 参照]

〈全身型若年性特発性関節炎〉

17.1.6 国内第Ⅲ相試験

全身型若年性特発性関節炎患者 19 例（16 歳以上の患者 2 例を含む）を対象とした非盲検、非対照試験（G1301 試験）で、本剤 1 回 4mg/kg（最高用量は 300mg）を 4 週毎に非盲検下で皮下投与した。その結果、8 週後の adapted ACR pediatric 30 を達成した患者の割合は 100%（19/19 例）であった。また、28 週後に経口副腎皮質ステロイド薬の減量が達成できた患者の割合は 73.7%（14/19 例）であった[9,10)]。

副作用は 19 例中 13 例（68.4%）に認められた。主な副作用は注射部位反応（3 例、15.8%）、肝機能異常、咽頭炎、アラニンアミノトランスフェラーゼ増加（各 2 例、10.5%）であった。

17.1.7 外国第Ⅲ相試験（プラセボ対照単回投与試験）

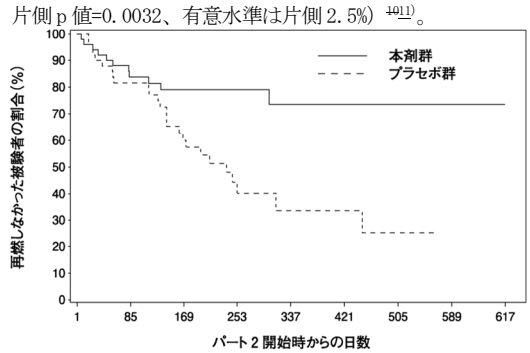
全身型若年性特発性関節炎患者 84 例（16 歳以上の患者 10 例を含む）を対象とした二重盲検比較試験（G2305 試験）で、本剤 1 回 4mg/kg（最高用量は 300mg）又はプラセボを二重盲検下で単回皮下投与した。その結果、15 日後の adapted ACR pediatric 30 を達成した患者の割合は、本剤群 83.7%（36/43 例）、プラセボ群 9.8%（4/41 例）であり、本剤群の割合はプラセボ群と比べて有意に高かった（Cochran-Mantel-Haenszel 検定、片側 p 値<0.0001、有意水準は片側 0.697%、O’Brien-Fleming 法により検定の多重性を調整）[10,11)]。

副作用は本剤群で 43 例中 5 例（11.6%）に認められた。本剤群で認められた副作用は、気管支肺炎、斑状丘疹状皮疹、貪食細胞性組織球症、肝炎、好中球減少症、白血球減少症、アレルギー性浮腫、頭痛、水痘、浮動性めまい、そう痒症（各 1 例、2.3%）であった。

17.1.8 外国第Ⅲ相試験（ランダム化投与中止試験）

全身型若年性特発性関節炎患者を対象とした G2301 試験で、パート 1［177 例（16 歳以上の患者 17 例を含む）］で本剤 1 回 4mg/kg（最高用量は 300mg）を非盲検下で 4 週毎に皮下投与した（非盲検期）。パート 1 に引き続いて実施したパート 2［100 例（16 歳以上の患者 11 例を含む）］では本剤 1 回 4mg/kg（最高用量は 300mg）又はプラセボを 1：1 の比（各 50 例）で割付し、二重盲検下で 4 週毎に皮下投与した（二

重盲検期）。その結果、パート 1 における経口副腎皮質ステロイド薬の減量が達成できた患者の割合は 44.5%(57/128 例)であった。また、パート 2 における再燃までの期間について、プラセボ群に対する本剤群のハザード比と 95%信頼区間は 0.36 (0.17, 0.75) であり、本剤群の再燃までの期間はプラセボ群と比べて有意に延長した（層別ログランク検定、片側 p 値=0.0032、有意水準は片側 2.5%）[10,11]。



Kaplan-Meier法で推定した再燃しなかった被験者の割合

パート 1（非盲検期）の副作用は 177 例中 30 例（16.9%）に認められた。主な副作用は、貪食細胞性組織球症（4 例、2.3%）、頭痛（3 例、1.7%）であった。

パート 2（二重盲検期）の副作用は本剤群で 50 例中 13 例（26.0%）に認められた。主な副作用は、上気道感染（3 例、6.0%）であった。

〈成人発症スチル病〉

17.1.9 国内第Ⅲ相試験

成人発症スチル病患者 14 例を対象とした非盲検、非対照試験（G1302 試験）で、本剤 1 回 4mg/kg（最高用量は 300mg）を 4 週毎に非盲検下で皮下投与した。その結果、有効性の主要解析対象 11 例において、副腎皮質ステロイド薬の増量又は静脈内投与をすることなく 8 週時点で adapted ACR 30 を達成した患者の割合［95%信頼区間］は、54.5%(6/11 例)［20.6, 88.5］と、95%信頼区間の下限値は事前に規定した閾値有効率 40%を下回った（正規近似による割合の検定，片側 p 値 0.249）。なお、本剤を投与した全例（14 例）における adapted ACR 30 を達成した患者の割合は 28 週、48 週時点でそれぞれ 75.0%(9/12 例)、81.8%（9/11 例）であった。また、経口副腎皮質ステロイド薬の減量が達成できた患者の割合は 28 週、48 週時点でそれぞれ 58.3%（7/12 例）、54.5%（6/11 例）であった[12]。

投与 48 週時点で副作用は 14 例中 7 例（50.0%）に認められた。2 例以上で発現した副作用は帯状疱疹（2 例、14.3%）であった。

18. 薬効薬理

18.1 作用機序

カナキヌマブ（遺伝子組換え）は、ヒト IL-1β 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。ヒト IL-1β に結合し、IL-1β が受容体に結合することを阻害することにより、その活性を中和する。

18.2 IL-1β 阻害作用

カナキヌマブ（遺伝子組換え）は、ヒト IL-1β に結合（解離定数：約 40pM）し、ヒト IL-1β とヒト IL-1 受容体との結合を阻害した[13,14]。

18.3 *In vitro* における薬理活性

カナキヌマブ（遺伝子組換え）は、ヒト IL-1β によるヒト皮膚線維芽細胞からの IL-6 産生及びヒト黒色腫細胞における IL-8 のプロモーター活性を抑制した[15,16]。

18.4 *In vivo* における薬理活性

カナキヌマブ（遺伝子組換え）は、ヒト IL-1β 誘発マウス関節炎の腫脹を単回腹腔内投与で抑制した[16,17]。また、ヒト IL-1β で誘発されるマウス空気嚢への好中球浸潤を単回腹腔内投与で抑制した[16,18]。更に、ヒト IL-1β により誘発されるラットの発熱を単回静脈内投与で抑制した[17,19]。

18.5 その他の作用

カナキヌマブ（遺伝子組換え）は、*in vitro* でヒト混合リンパ球反応における T 細胞増殖を阻害しなかった[18,20]。

19. 有効成分に関する理化学的知見

一般的名称

カナキヌマブ（遺伝子組換え）

Canakinumab (Genetical Recombination)

分子量

約 148,000

本質

ヒト IL-1β に対する遺伝子組換えヒト IgG1 モノクローナル抗体であり、マウスハイブリドーマ細胞 Sp2/0-Ag14 により産生される 448 個のアミノ酸残基からなる重鎖（$C_{2196}H_{3387}N_{587}O_{669}S_{16}$；分子量：49,227.96）2 分子及び 214 個のアミノ酸残基からなる軽鎖（$C_{1030}H_{1596}N_{274}O_{336}S_5$；分子量：23,353.65）2 分子で構成される糖蛋白質

20. 取扱い上の注意

外箱開封後は遮光して保存すること。

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

21.2 国内での治験症例が極めて限られていることから、再審査期間又は一定数の症例に係るデータが蓄積されるまでの間は、本剤投与症例全例を登録して安全性及び有効性に関する製造販売後調査を実施すること。その中で、感染症等の発現を含めた長期投与時の安全性及び有効性について十分に検討すること。

22. 包装

1 バイアル

23. 主要文献

1）社内資料：日本人健康成人男子を対象とした単回投与試験（A1101）（2011 年 9 月 26 日承認、CTD2.7.6.2.1.1）［20114619］

2）社内資料：外国人クリオピリン関連周期性症候群患者を対象とした第Ⅱ相試験（A2102）（2011 年 9 月 26 日承認、CTD2.7.6.4.2.2）［20114620］

3）社内資料：母集団薬物動態解析（2016 年 12 月 19 日承認、CTD2.7.2.2.4）［20160943］

4）社内資料：全身型若年性特発性関節炎患者を対象とした母集団薬物動態解析（2018 年 7 月 2 日承認、CTD2.7.2.3.1）［20180287］

5）社内資料：成人発症スチル病患者を対象とした母集団薬物動態解析（CTD2.5.3.1.3）［XXXXXXXX］

~~5~~6）Imagawa,T.et al.：Clin.Exp.Rheumatol. 2013；31（2）：302-309［20131638］

~~6~~7）Lachmann,H.J.et al.：New Engl.J.Med. 2009；360（23）：2416-2425［20114320］

~~7~~8）Kuemmerle-Deschner,J.B.et al.：Ann.Rheum.Dis. 2011；70（12）：2095-2102［20114240］

~~8~~9）社内資料：周期性発熱症候群患者を対象とした国際共同試験（N2301、二重盲検期）（2016 年 12 月 19 日承認、CTD2.7.6.4.1.1）［20160944］

~~9~~10）社内資料：全身型若年性特発性関節炎患者を対象とした国内第 III 相臨床試験（G1301 試験）（2018 年 7 月 2 日承認、CTD2.7.6.4.2.4）［20180272］

~~10~~11）Ruperto, N. et al.：New Engl.J.Med. 2012；367（25）：2396-2406［20180289］

12）社内資料：成人発症スチル病患者を対象とした国内第 III 相臨床試験（G1302 試験）（CTD2.7.6.4.2）［XXXXXXXX］

~~11~~13）社内資料：ヒト IL-1β に対する結合親和性（2011 年 9 月 26 日承認、CTD2.6.2.2.1.1）［20114621］

~~12~~14）社内資料：ヒト IL-1β の受容体との結合に対する阻害作用（2011 年 9 月 26 日承認、CTD2.6.2.2.1.4）［20114622］

~~13~~15）社内資料：ヒト IL-1β によるヒト皮膚線維芽細胞からの IL-6 産生に対する抑制作用（2011 年 9 月 26 日承認、CTD2.6.2.2.2.1）［20114623］

~~14~~16）社内資料：ヒト IL-1β によるヒト黒色腫細胞の IL-8 プロモーター活性に対する抑制作用（2011 年 9 月 26 日承認、CTD2.6.2.2.2.3）［20114624］

~~15~~17）社内資料：ヒト IL-1βによるマウス膝関節の腫脹に対する抑制作用　（2011 年 9 月 26 日承認、CTD2.6.2.2.3.1）［20114625］

~~16~~18）社内資料：ヒト IL-1βによるマウス空気嚢への好中球浸潤に対する抑制作用　（2011 年 9 月 26 日承認、CTD2.6.2.2.3.2）［20114626］

~~17~~19）社内資料：ヒト IL-1βによるラット発熱に対する抑制作用（2011 年 9 月 26 日承認、CTD2.6.2.2.3.3）［20114627］

~~18~~20）社内資料：ヒト混合リンパ球反応に対する作用　（2011 年 9 月 26 日承認、CTD2.6.2.3.1.1）［20114628］

24. 文献請求先及び問い合わせ先

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（祝日及び当社休日を除く）
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26. 製造販売業者等

26.1 製造販売

ノバルティス ファーマ株式会社
東京都港区虎ノ門 1－23－1

(06)

＜参考＞

イラリス®皮下注射液150mg投与液量一覧表

クリオピリン関連周期性症候群、高IgD症候群（メバロン酸キナーゼ欠損症）、TNF受容体関連周期性症候群、家族性地中海熱

体重40kg以下の患者に対する投与液量=用量レベル×患者の体重÷投与濃度

用量レベル=１回２mg/kg（体重40kg以下の患者）
１回150mg　（体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）１回投与用量	投与液量	投与濃度※
8 kg	16mg	0.11mL	150mg/mL
10kg	20mg	0.13mL	
12kg	24mg	0.16mL	
14kg	28mg	0.19mL	
16kg	32mg	0.21mL	
18kg	36mg	0.24mL	
20kg	40mg	0.27mL	
22kg	44mg	0.29mL	
24kg	48mg	0.32mL	
26kg	52mg	0.35mL	
28kg	56mg	0.37mL	
30kg	60mg	0.40mL	
32kg	64mg	0.43mL	
34kg	68mg	0.45mL	
36kg	72mg	0.48mL	
38kg	76mg	0.51mL	
40kg	80mg	0.53mL	
>40kg	150mg	1.0mL	

用量レベル=１回６mg/kg（体重40kg以下の患者）
１回450mg　（体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）１回投与用量	投与液量	投与濃度※
8 kg	48mg	0.32mL	150mg/mL
10kg	60mg	0.40mL	
12kg	72mg	0.48mL	
14kg	84mg	0.56mL	
16kg	96mg	0.64mL	
18kg	108mg	0.72mL	
20kg	120mg	0.80mL	
22kg	132mg	0.88mL	
24kg	144mg	0.96mL	
26kg	156mg	1.04mL	
28kg	168mg	1.12mL	
30kg	180mg	1.20mL	
32kg	192mg	1.28mL	
34kg	204mg	1.36mL	
36kg	216mg	1.44mL	
38kg	228mg	1.52mL	
40kg	240mg	1.60mL	
>40kg	450mg	3.0mL	

用量レベル=１回４mg/kg（体重40kg以下の患者）
１回300mg　（体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）１回投与用量	投与液量	投与濃度※
8 kg	32mg	0.21mL	150mg/mL
10kg	40mg	0.27mL	
12kg	48mg	0.32mL	
14kg	56mg	0.37mL	
16kg	64mg	0.43mL	
18kg	72mg	0.48mL	
20kg	80mg	0.53mL	
22kg	88mg	0.59mL	
24kg	96mg	0.64mL	
26kg	104mg	0.69mL	
28kg	112mg	0.75mL	
30kg	120mg	0.80mL	
32kg	128mg	0.85mL	
34kg	136mg	0.91mL	
36kg	144mg	0.96mL	
38kg	152mg	1.01mL	
40kg	160mg	1.07mL	
>40kg	300mg	2.0mL	

用量レベル=１回８mg/kg（体重40kg以下の患者）
１回600mg　（体重40kgを超える患者）

体重	カナキヌマブ（遺伝子組換え）１回投与用量	投与液量	投与濃度※
8 kg	64mg	0.43mL	150mg/mL
10kg	80mg	0.53mL	
12kg	96mg	0.64mL	
14kg	112mg	0.75mL	
16kg	128mg	0.85mL	
18kg	144mg	0.96mL	
20kg	160mg	1.07mL	
22kg	176mg	1.17mL	
24kg	192mg	1.28mL	
26kg	208mg	1.39mL	
28kg	224mg	1.49mL	
30kg	240mg	1.60mL	
32kg	256mg	1.71mL	
34kg	272mg	1.81mL	
36kg	288mg	1.92mL	
38kg	304mg	2.03mL	
40kg	320mg	2.13mL	
>40kg	600mg	4.0mL	

※本剤は、注射液吸引時の損失を考慮し、１バイアルから150mgを注射するに足る量を確保するために過量充填されている。
１回投与量が150mgを超える場合は、２バイアル以上が必要となる。

全身型若年性特発性関節炎、成人発症スチル病

投与液量=用量レベル×患者の体重÷投与濃度

用量レベル= 1 回 4mg/kg
最高用量 1 回 300mg

体重	カナキヌマブ（遺伝子組換え）1 回投与用量	投与液量	投与濃度※
8 kg	32mg	0.21mL	150mg/mL
10kg	40mg	0.27mL	
12kg	48mg	0.32mL	
14kg	56mg	0.37mL	
16kg	64mg	0.43mL	
18kg	72mg	0.48mL	
20kg	80mg	0.53mL	
22kg	88mg	0.59mL	
24kg	96mg	0.64mL	
26kg	104mg	0.69mL	
28kg	112mg	0.75mL	
30kg	120mg	0.80mL	
32kg	128mg	0.85mL	
34kg	136mg	0.91mL	
36kg	144mg	0.96mL	
38kg	152mg	1.01mL	
40kg	160mg	1.07mL	
42kg	168mg	1.12mL	
44kg	176mg	1.17mL	
46kg	184mg	1.23mL	
48kg	192mg	1.28mL	
50kg	200mg	1.33mL	
52kg	208mg	1.39mL	
54kg	216mg	1.44mL	
56kg	224mg	1.49mL	
58kg	232mg	1.55mL	
60kg	240mg	1.60mL	
62kg	248mg	1.65mL	
64kg	256mg	1.71mL	
66kg	264mg	1.76mL	
68kg	272mg	1.81mL	
70kg	280mg	1.87mL	
72kg	288mg	1.92mL	
74kg	296mg	1.97mL	
>=75kg	300mg	2.00mL	

※本剤は、注射液吸引時の損失を考慮し、1 バイアルから 150mg を注射するに足る量を確保するために過量充填されている。
1 回投与量が 150mg を超える場合は、 2 バイアル以上が必要となる。

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1 効能又は効果（案）及びその設定根拠

1.1 効能又は効果（案）

○以下のクリオピリン関連周期性症候群
・家族性寒冷自己炎症症候群
・マックル・ウェルズ症候群
・新生児期発症多臓器系炎症性疾患
○高 IgD 症候群（メバロン酸キナーゼ欠損症）
○TNF 受容体関連周期性症候群
既存治療で効果不十分な下記疾患
○家族性地中海熱
○全身型若年性特発性関節炎
○成人発症スチル病

1.2 効能又は効果（案）の設定根拠

成人発症スチル病（AOSD）は，成人期（16 歳以上）に初めて発症する，小児のスチル病［現在の全身型若年性特発性関節炎（SJIA）］と似た症状を呈する炎症性疾患である。AOSD 及び SJIA が成人期（16 歳以上）まで遷延した又は成人期に再発した患者（以下，SJIA 成人移行例）を総称して，成人スチル病（ASD）と呼ぶ。AOSD は国内で難病指定されている希少疾患である。カナキヌマブは国内で 2018 年 7 月に SJIA の適応を取得しており，ASD 患者のうち SJIA の成人移行例については臨床使用可能である。今般，ステロイドで効果不十分な AOSD 患者を対象とした国内第 III 相試験（G1302 試験）成績が得られたことから，G1302 試験，外国医師主導試験（GDE01T 試験）成績ならびに SJIA を対象とした国内外の試験の併合解析データに基づいて，AOSD 患者における本剤の有効性及び安全性を評価した。

G1302 試験，GDE01T 試験，及び SJIA 併合データの結果から，カナキヌマブ投与により，ステロイドで治療しても活動性を示す AOSD 患者の疾患活動性，炎症所見及び臨床症状（関節症状，全身症状）を迅速かつ持続的に改善するとともにステロイドの減量が可能となることが示された（2.5-6.2 項）。また，G1302 試験の結果から日本人 AOSD 患者に対してカナキヌマブは良好な安全性プロファイルを示した。長期投与による有害事象の発現割合の増加も認められず，新たな安全性シグナルは特定されなかった。SJIA の成人移行例においても同様の安全性プロファイルが示されている（2.5-5.7 項）。

以上の AOSD を対象とした臨床試験及び既承認の SJIA を対象とした併合解析に基づく結果を踏まえ，既存治療で効果不十分な成人発症スチル病を効能又は効果（案）として設定した。

2 効能又は効果に関連する注意（案）

2.1 効能又は効果に関連する注意（案）

〈家族性地中海熱〉

5.1 コルヒチン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。

〈全身型若年性特発性関節炎及び成人発症スチル病〉

5.2 副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。

5.3 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MAS を合併している患者では MAS に対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中に MAS が発現した場合は、休薬を考慮し、速やかに MAS に対する適切な治療を行うこと。

2.2 効能又は効果に関連する注意（案）の設定根拠

(1) 副腎皮質ステロイド薬による適切な治療を行っても、効果不十分な場合に投与すること。

AOSD の第一選択薬は副腎皮質ステロイド（以下，ステロイド）であり，ほとんどの患者では単球・マクロファージの活性化の抑制を目的としたステロイドの全身投与が行われる。疾患活動性が制御［臨床症状（関節及び全身症状）の改善及び炎症所見の正常化］できればステロイドを徐々に減量するが，減量中又は一定用量での維持療法中に再燃する患者も少なくない。減量に難渋する場合や再燃を繰り返す等のステロイド治療抵抗性の患者では，疾患活動性／臨床症状の改善及びステロイドの減量を目的としてメトトレキサート（MTX）の併用が強く推奨されている。しかし，MTX は国内では AOSD に対する保険適用がなく，また特有の副作用（消化器症状，肝障害等）が知られていることから，使用にあたっては注意を払う必要がある。MTX が禁忌若しくは MTX 併用でも十分な治療効果が得られない場合はシクロスポリン等の免疫抑制薬の併用投与が有用な場合があるが，エビデンスレベルが低く，国内では保険適用がない。ステロイド治療抵抗性や MTX 治療抵抗性の患者に対しては生物学的製剤の使用が考慮される。成人スチル病診療ガイドラインでは，IL-1 阻害薬，IL-6 阻害薬，TNF 阻害薬等の生物学的製剤が治療抵抗性 AOSD に有用であることが提案されているが，国内で AOSD に対して保険適用のある生物学的製剤は IL-6 阻害薬のトシリズマブのみである（2.5-1.1.2 項）。

G1302 試験では，ステロイド治療抵抗性日本人 AOSD 患者に対する有効性及び安全性が示されていることに加え，組み入れられた被験者の約半数がトシリズマブの治療歴のある被験者であったが，トシリズマブの治療歴の有無にかかわらず有効性が示されている。また，GDE01T 試験においても，外国人 AOSD 患者に対する有効性及び安全性が示されており，組み入れられた被験者の約 7～8 割が生物学的製剤の治療歴のある被験者であったが，生物学的製剤の治療歴の有無にかかわらず，有効性が示されている（2.5-6.2.3 項）。

以上のとおり，AOSD に対する治療の現状，及び AOSD を対象とした臨床試験成績に基づき，生物学的製剤の治療歴の有無にかかわらずステロイド治療で効果不十分な患者集団を対象とすることが適切と考え，SJIA と同様に本記載を設定した。

(2) 重篤な合併症としてマクロファージ活性化症候群（MAS）を発症することがある。MAS を合併している患者では MAS に対する治療を優先させ本剤の投与を開始しないこと。また、本剤投与中に MAS が発現した場合は、休薬を考慮し、速やかに MAS に対する適切な治療を行うこと。

MAS は高サイトカイン血症によるマクロファージの異常活性化により血球貪食をきたす病態であり，発熱，肝脾腫，汎血球減少，肝機能障害，高フェリチン血症，血球貪食像等の臨床像を呈する。MAS は AOSD の 10%～15%に合併し，SJIA を対象とした調査では発症の契機は疾患活動性の増悪が 52%，感染症が 34%と報告されている（2.5-6.3 項）。

G1302 試験では，注目すべき有害事象の「MAS」として，潜在的に MAS の可能性がある関連する PT をグループ化して評価した（2.5-5.1.1 項）。関連する PT として特定されている譫妄（中等度）が 1 名に発現したが，事象発現前後の検査では血球減少，肝機能検査値異常，フェリチンの高値等の臨床像は認められなかったことから，MAS ではないと判断した。発現 6 日後には治験薬の投与を変更することなく事象は消失し，治験薬との関連はなしと判断された。GDE01T 試験では，「MAS」の発現はなかった。SJIA 併合データの解析では 16 歳以上と他の年齢区分で「MAS」の発現割合に大きな違いはみられず，G1302 試験の結果とも違いはなかった（2.5-6.3 項）。

既承認適応と比較して MAS に関する新たな懸念は認められなかったが，MAS は AOSD の重篤な合併症であり，発症した場合に死亡に至る恐れがあること，また AOSD は SJIA と疾患概念及び治療法が類似する疾患であることから，SJIA と同様に本記載を設定した。

3 用法及び用量（案）及びその設定根拠

3.1 用法及び用量（案）

〈クリオピリン関連周期性症候群〉

通常、体重 40kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2mg/kg を、体重 40kg を超える患者には 1 回 150mg を 8 週毎に皮下投与する。

十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが、1 回最高用量は体重 40kg 以下の患者では 8mg/kg、体重 40kg を超える患者では 600mg とする。

最高用量まで増量し、8 週以内に再燃がみられた場合には、投与間隔を 4 週間まで短縮できる。

なお、症状に応じて 1 回投与量の増減を検討すること。

〈高 IgD 症候群（メバロン酸キナーゼ欠損症）〉

通常、体重 40kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2mg/kg を、体重 40kg を超える患者には 1 回 150mg を、4 週毎に皮下投与する。
十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40kg 以下の患者では 6mg/kg、体重 40kg を超える患者では 450mg とする。
〈TNF 受容体関連周期性症候群及び家族性地中海熱〉
通常、体重 40kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2mg/kg を、体重 40kg を超える患者には 1 回 150mg を、4 週毎に皮下投与する。
十分な臨床的効果がみられない場合には追加投与又は適宜漸増するが、1 回最高用量は体重 40kg 以下の患者では 4mg/kg、体重 40kg を超える患者では 300mg とする。
〈全身型若年性特発性関節炎及び成人発症スチル病〉
通常、カナキヌマブ（遺伝子組換え）として 1 回 4mg/kg を、4 週毎に皮下投与する。1 回最高用量は 300mg とする。

3.2 用法及び用量（案）の設定根拠

本用法及び用量は，主に日本人 AOSD 患者を対象とした G1302 試験の用法及び用量に基づいて設定した。本用法及び用量は，既承認の SJIA の用法及び用量，並びに欧米でスチル病の適応に対して承認された用法及び用量と同一である。

G1302 試験の用法及び用量は，以下の根拠に基づき設定された（2.5-4.2.1 項）。

- SJIA 患者を対象に実施された国内外の臨床試験及び市販後データでは，当該用法及び用量の安全性プロファイルは良好で，日本人患者と非日本人患者で有効性，安全性，及び PK/PD に明らかな差は認められていないこと。
- SJIA 患者を対象とした当該用法及び用量を用いた臨床試験の併合データの結果から，年齢区分を問わず，カナキヌマブの有効性及び安全性が確認されたこと。
- 外国人 AOSD 患者を対象とした GDE01T 試験において本用法及び用量での有効性及び良好な安全性プロファイルが示されたこと

G1302 試験において，日本人 AOSD 患者に対するカナキヌマブの有効性及び良好な安全性プロファイルが確認された。また，SJIA 併合データでは，SJIA の成人移行例における有効性及び安全性が示された。

以上より，日本人 AOSD 患者に対して当該用法及び用量を設定することが適切と考えた。

4 用法及び用量に関連する注意（案）

本承認申請に伴う用法及び用量に関連する使用上の注意の追加及び変更はない。

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1 使用上の注意（案）及びその設定根拠

今回の適応追加の承認申請に際し，成人発症スチル病（以下，AOSD）患者を対象とした国内第 III 相試験（G1302 試験）及び外国医師主導第 II 相試験（GDE01T 試験）で，有効性及び安全性を検討した。

使用上の注意（案）は，2021 年 11 月改訂の添付文書，G1302 試験及び GDE01T 試験の結果を基に総合的に勘案し，作成した。

G1302 試験及び GDE01T 試験では，既承認の適応症に対する使用経験より特定された安全性プロファイルと比較して，AOSD 患者特有の新たな安全性の懸念は認められなかったことから，「11.副作用」以外の使用上の注意に関する変更は不要と判断した。

2 「11.副作用」欄

2.1 「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 重篤な感染症（~~10.2~~12.7%）

敗血症や日和見感染症（アスペルギルス症、非定型抗酸菌症、帯状疱疹等）等の重篤な感染症があらわれることがある。［1.1、1.2、2.1、8.1、8.2、9.1.1、9.1.3、9.1.4 参照］

11.1.2 好中球減少（頻度不明）

［8.4 参照］

11.2 その他の副作用

	5%以上	5%未満	頻度不明
感染症	鼻咽頭炎	胃腸炎、肺炎、副鼻腔炎、上気道感染、咽頭炎、尿路感染	~~尿路感染、~~気管支炎、ウイルス感染、扁桃炎、鼻炎、耳感染、外陰部膣カンジダ症、下気道感染、肺感染
神経系	－	頭痛	回転性めまい
過敏症	~~－~~過敏症反応	－	~~過敏症反応~~
皮膚	注射部位反応	－	－
消化器	－	口内炎、下痢	~~下痢、~~腹痛
肝臓	－	AST・ALT 上昇	－

血液	－	白血球数減少	血小板数減少
その他	－	－	体重増加

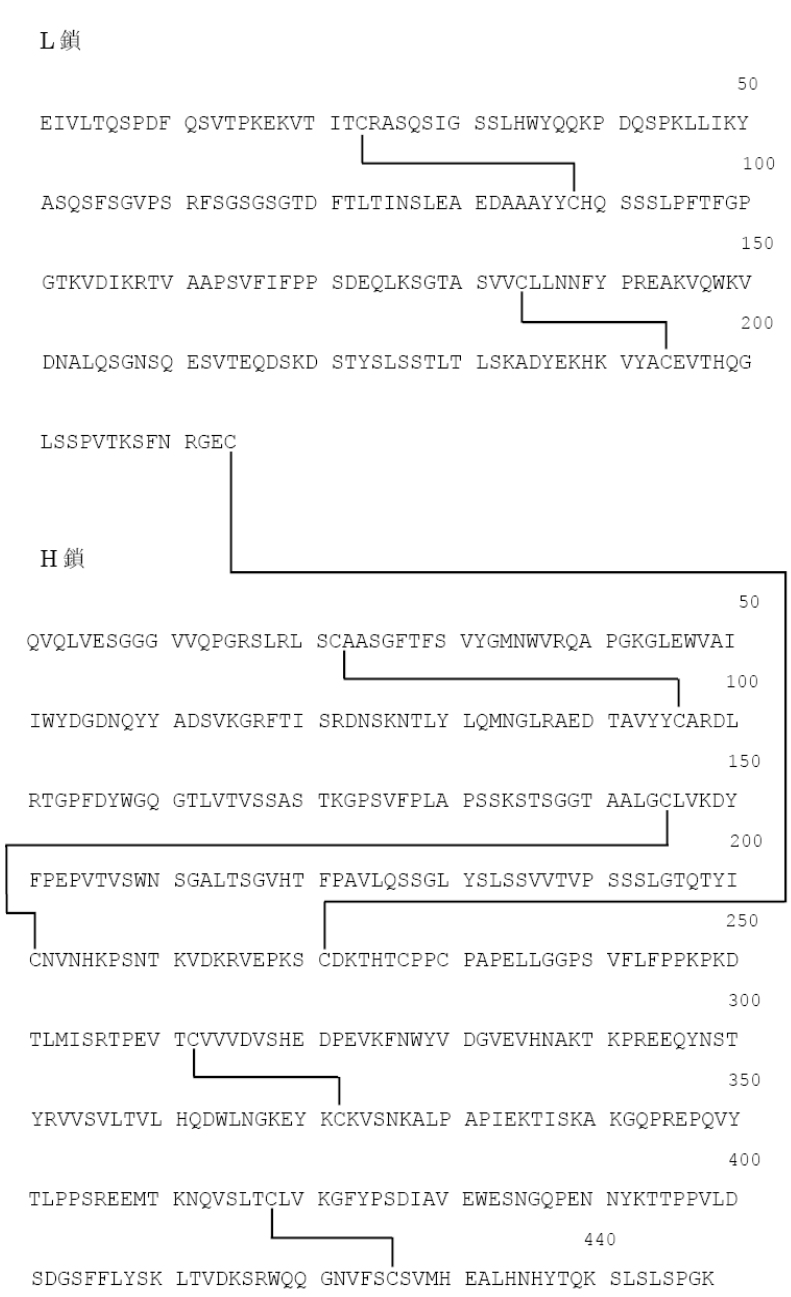
2.2 「11.副作用」の設定根拠

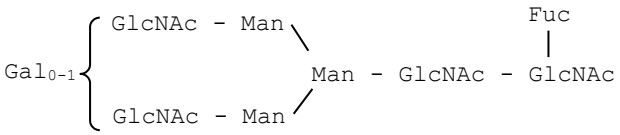
AOSD 患者に特有の新たな安全性の懸念は認められず，既存の安全性プロファイルと一貫していたことから，現行添付文書に基づき設定した。発現頻度は，クリオピリン関連周期性症候群の効能取得時の評価試験である D2308 試験，高 IgD 症候群（メバロン酸キナーゼ欠損症）・TNF 受容体関連周期性症候群・家族性地中海熱の効能取得時の評価試験である N2301 試験（日本人集団），全身型若年性特発性関節炎の効能取得時の評価試験である G1301 試験，本申請の評価試験である G1302 試験の併合解析結果に基づき変更した。

1.9 一般的名称に係る文書

既承認医薬品に係る資料を参照

〈現行〉

化学名・別名	カナキヌマブは，ヒトインターロイキン-1ß 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。 カナキヌマブは，マウスハイブリドーマ細胞 Sp2/0-Ag14 で産生される。 カナキヌマブは，448 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：約 148,000）である。
構　造　式	 H 鎖 Q1：ピログルタミン酸， K448 ：部分的プロセシング N298：糖鎖結合部位 主糖鎖構造

	 分子内ジスルフィド結合 L 鎖 C23-L 鎖 C88，L 鎖 C134-L 鎖 C194，H 鎖 C22-H 鎖 C96，H 鎖 C145-H 鎖 C201， H 鎖 C262-H 鎖 C322，H 鎖 C368-H 鎖 C426 分子間ジスルフィド結合 L 鎖 C214-H 鎖 C221，H 鎖 C227-H 鎖 C227，H 鎖 C230-H 鎖 C230
効能・効果	1. 以下のクリオピリン関連周期性症候群 ・ 家族性寒冷自己炎症症候群 ・ マックル・ウェルズ症候群 ・ 新生児期発症多臓器系炎症性疾患 2. 高 IgD 症候群（メバロン酸キナーゼ欠損症） 3. TNF 受容体関連周期性症候群 4. 既存治療で効果不十分な下記疾患 家族性地中海熱 全身型若年性特発性関節炎
用法・用量	1. クリオピリン関連周期性症候群 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。 十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。 最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。 なお，症状に応じて 1 回投与量の増減を検討すること。 2. 高 IgD 症候群（メバロン酸キナーゼ欠損症） 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。 十分な臨床効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg，体重 40 kg を超える患者では 450 mg とする。 3. TNF 受容体関連周期性症候群及び家族性地中海熱 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。 十分な臨床効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg，体重 40 kg を超える患者では 300 mg とする。 4. 全身型若年性特発性関節炎 通常，カナキヌマブ（遺伝子組換え）として 1 回 4 mg/kg を，4 週毎に皮下投与する。 1 回最高用量は 300 mg とする。
劇薬等の指定	生物由来製品 劇薬：原体・製剤

<table>
<tr><td></td><td>処方箋医薬品</td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：カナキヌマブ（遺伝子組換え）
製剤：イラリス皮下注用 150 mg
［1 バイアル中の含有量：カナキヌマブ（遺伝子組換え）180.0 mg］
［日本薬局方「注射用水」1.0 mL で溶解した溶液 1.0 mL に含まれる量：カナキヌマブ（遺伝子組換え）150.0 mg］
製剤：イラリス皮下注射液 150 mg
［1 mL 中の含有量：カナキヌマブ（遺伝子組換え）150.0 mg］</td></tr>
<tr><td>毒性</td><td>単回投与毒性試験
<table>
<tr><td>動物種</td><td>静脈内</td><td>皮下</td></tr>
<tr><td>マーモセット ♂♀</td><td>100 mg/kg まで死亡はみられず</td><td>150 mg/kg まで死亡はみられず</td></tr>
</table>
単回投与毒性試験は実施していないため，反復投与毒性試験の結果から記載した。

反復投与毒性試験
<table>
<tr><td>動物種</td><td>投与期間</td><td>投与経路</td><td>投与量 (mg/kg)</td><td>無毒性量 (mg/kg)</td><td>主な所見</td></tr>
<tr><td>マーモセット</td><td>試験 1 日及び 43 日</td><td>皮下</td><td>5，50 及び 150</td><td>150</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>13 週間，週 2 回</td><td>皮下</td><td>15，50 及び 150</td><td>150</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>28 日間，週 2 回</td><td>静脈内</td><td>10，30 及び 100</td><td>100</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
<tr><td>マーモセット</td><td>26 週間，週 2 回</td><td>静脈内</td><td>10，30 及び 100</td><td>100</td><td>カナキヌマブの投与に起因した毒性所見なし</td></tr>
</table></td></tr>
<tr><td>副作用</td><td>【クリオピリン関連周期性症候群患者対象の国内臨床試験】
副作用発現率 12/19 = 63.2%
主な副作用の種類 例数
鼻咽頭炎 3
口内炎 2
【海外クリオピリン関連周期性症候群患者対象臨床試験結果併合集計】
副作用発現率 68/169 = 40.2%
主な副作用の種類 例数
体重増加 7
頭痛 7
回転性めまい 6
気管支炎 5
（承認時までの集計）

【高 IgD 症候群（メバロン酸キナーゼ欠損症）患者，TNF 受容体関連周期性症候群患者，家族性地中海熱患者対象国際共同治験】
副作用発現率 47/169（日本人 8 例含む）=27.8%</td></tr>
</table>

	主な副作用の種類 例数 注射部位反応 13 頭痛 5 （効能又は効果の一変承認時までの集計） 【全身型若年性特発性関節炎患者対象の国内臨床試験】 副作用発現率 13/19 = 68.4% 主な副作用の種類 例数 注射部位反応 3 【海外全身型若年性特発性関節炎患者対象臨床試験結果併合集計】 副作用発現率 128/324 = 39.5% 主な副作用の種類 例数 鼻咽頭炎 14 （効能又は効果の一変承認時までの集計）
会　　社	ノバルティスファーマ株式会社 製剤：製造販売（輸入）

〈追加・変更〉(下線部)

化学名・別名	
構　造　式	
効能・効果	1. 以下のクリオピリン関連周期性症候群 ・ 家族性寒冷自己炎症症候群 ・ マックル・ウェルズ症候群 ・ 新生児期発症多臓器系炎症性疾患 2. 高 IgD 症候群（メバロン酸キナーゼ欠損症） 3. TNF 受容体関連周期性症候群 4. 既存治療で効果不十分な下記疾患 家族性地中海熱 全身型若年性特発性関節炎 <u>成人発症スチル病</u>
用法・用量	1. クリオピリン関連周期性症候群 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を 8 週毎に皮下投与する。 十分な臨床的効果（皮疹及び炎症症状の寛解）がみられない場合には適宜漸増する が，1 回最高用量は体重 40 kg 以下の患者では 8 mg/kg，体重 40 kg を超える患者では 600 mg とする。 最高用量まで増量し，8 週以内に再燃がみられた場合には，投与間隔を 4 週間まで短縮できる。 なお，症状に応じて 1 回投与量の増減を検討すること。 2. 高 IgD 症候群（メバロン酸キナーゼ欠損症） 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。 十分な臨床効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 6 mg/kg，体重 40 kg を超える患者では 450 mg とする。

	3. TNF 受容体関連周期性症候群及び家族性地中海熱 通常，体重 40 kg 以下の患者にはカナキヌマブ（遺伝子組換え）として 1 回 2 mg/kg を，体重 40 kg を超える患者には 1 回 150 mg を，4 週毎に皮下投与する。 十分な臨床効果がみられない場合には追加投与又は適宜漸増するが，1 回最高用量は体重 40 kg 以下の患者では 4 mg/kg，体重 40 kg を超える患者では 300 mg とする。 4. 全身型若年性特発性関節炎及び成人発症スチル病 通常，カナキヌマブ（遺伝子組換え）として 1 回 4 mg/kg を，4 週毎に皮下投与する。1 回最高用量は 300 mg とする。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	【クリオピリン関連周期性症候群患者対象の国内臨床試験】 副作用発現率 12/19 = 63.2% 主な副作用の種類 例数 鼻咽頭炎 3 口内炎 2 【海外クリオピリン関連周期性症候群患者対象臨床試験結果併合集計】 副作用発現率 68/169 = 40.2% 主な副作用の種類 例数 体重増加 7 頭痛 7 回転性めまい 6 気管支炎 5 （承認時までの集計） 【高 IgD 症候群（メバロン酸キナーゼ欠損症）患者，TNF 受容体関連周期性症候群患者，家族性地中海熱患者対象国際共同治験】 副作用発現率 47/169（日本人 8 例含む）=27.8% 主な副作用の種類 例数 注射部位反応 13 頭痛 5 （効能又は効果の一変承認時までの集計） 【全身型若年性特発性関節炎患者対象の国内臨床試験】 副作用発現率 13/19 = 68.4% 主な副作用の種類 例数 注射部位反応 3 【海外全身型若年性特発性関節炎患者対象臨床試験結果併合集計】 副作用発現率 128/324 = 39.5% 主な副作用の種類 例数 鼻咽頭炎 14 （効能又は効果の一変承認時までの集計）

	【成人発症スチル病患者対象の国内臨床試験】 副作用発現率 7/14 = 50.0% 主な副作用の種類 例数 帯状疱疹 2 （効能又は効果の一変承認時までの集計）
会　　社	

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1 第 3 部

該当資料なし

2 第 4 部

該当資料なし

3 第 5 部

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.2 全臨床試験一覧表							
5.2	－	全臨床試験一覧表	－	－	国内	評価	－
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							
－	該当なし	－	－	－	－	－	－
5.3.1.4 生物学的及び理化学的分析法検討報告書							
－	該当なし	－	－	－	－	－	－
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							

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
―	該当なし	―	―	―	―	―	―
5.3.2.2 肝代謝及び薬物相互作用試験報告書							
―	該当なし	―	―	―	―	―	―
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							
―	該当なし	―	―	―	―	―	―
5.3.3.3 内因性要因を検討した PK 試験報告書							
―	該当なし	―	―	―	―	―	―
5.3.3.4 外因性要因を検討した PK 試験報告書							
―	該当なし	―	―	―	―	―	―
5.3.3.5 ポピュレーション PK 試験報告書							
5.3.3.5-1	CACZ885A2203; CACZ885G2305; CACZ885G2301; CACZ885G2301E1; CACZ885G2306; CACZ885G1301; CACZ885GDE01T	Comparison of the pharmacokinetics and pharmacodynamics of canakinumab between patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD)	2024 年 4 月 12 日	ノバルティス	海外	評価	あり

添付資料番号	Report No./Study No.	表 題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.3.5-2	CACZ885G2301E1; CACZ885G1301; CACZ885G2306; CACZ885GDE01T; CACZ885G1302	Comparison of the pharmacokinetics of canakinumab (ACZ885) between patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and Japanese and non-Japanese patients with Adult-Onset Still's Disease (AOSD)	2024 年 4 月 9 日	ノバルティス	海外	評価	あり
5.3.3.5-3	CACZ885G2301E1; CACZ885G1301; CACZ885G2306; CACZ885GDE01T; CACZ885G1302	Comparison of the pharmacokinetics of canakinumab (ACZ885) between patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and Japanese and non-Japanese Adult-Onset Still's Disease (AOSD)	2024 年 7 月 30 日	ノバルティス	海外	評価	なし
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							
－	該当なし	－	－	－	－	－	－
5.3.4.2 患者における PD 試験及び PK/PD 試験報告書							
－	該当なし	－	－	－	－	－	－

添付資料番号	表題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
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	ACZ885GDE01T 総括報告書	2012 年 6 月～2018 年 5 月	ドイツ	海外	評価	あり
	ACZ885GDE01T Amendment 1	－	－	－	－	あり
5.3.5.2 非対照試験報告書						
5.3.5.2-1	ACZ885G1302 総括報告書	2021 年 3 月～20[redacted] 年[redacted]月（データカットオフ日）本報告時点で継続中	日本	国内	評価	あり
	ACZ885G1302 W48 総括報告書	2021 年 3 月～20[redacted] 年[redacted]月（データカットオフ日）本報告時点で継続中	日本	国内	評価	あり
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	SCE Appendix 1 (Integrated Summary of Efficacy, data analyses)	－	－	－	－	－
5.3.5.3-2	SCS Appendix 1 (Integrated Summary of Safety, data analyses)	－	－	－	－	－
5.3.5.3-3	SCE JP Appendix 1-1 (Integrated Summary of Efficacy, data analyses)	－	－	－	－	－
	SCE JP Appendix 1-2 (Integrated Summary of Efficacy, data analyses)	－	－	－	－	－
5.3.5.3-4	SCS JP Appendix 1-1 (Integrated Summary of Safety, data analyses)	－	－	－	－	－
	SCS JP Appendix 1-2 (Integrated Summary of Safety, data analyses)	－	－	－	－	－
5.3.5.4 その他の臨床試験報告書						

添付資料番号	表題	試験実施期間	試験実施場所	報種類（国内／海外）	評価／参考	電子データの提出
5.3.5.4-1	Canakinumab treatment of active Still's disease including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) Systematic review of scientific literature on i) the relationship between adult-onset Still's disease and systemic juvenile idiopathic arthritis, and ii) the evidence for IL-1 inhibition in the treatment of adult-onset Still's disease	—	—	—	—	—
5.3.6　市販後の使用経験に関する報告書						
5.3.6-1	PERIODIC SAFETY UPDATE REPORT (01 Jul 2018 - 30 Jun 2021)	—	—	—	—	—
5.3.6-2	PERIODIC SAFETY UPDATE REPORT (01 Jul 2021 - 30 Jun 2024)	—	—	—	—	—
5.3.7　患者データ一覧表及び症例記録						
—	該当なし	—	—	—	—	—

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
5.4 参考文献　（評価／参考の別：参考資料）		
—	Adachi S, Takase-Minegishi K, Maeda A, et al. (2023) Risk of Macrophage Activation Syndrome in Patients with Adult-Onset Still's Disease Treated with IL-1 and IL-6 Inhibitors: A Meta-analysis and Single-Center Experience. Rheumatol Ther; 10(6):1623-36.	海外
—	Asanuma YF, Mimura T, Tsuboi H, et al. (2015) Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. Mod Rheumatol; 25(3):393-400.	海外
—	Bywaters EG (1971) Still's disease in the adult. Ann Rheum Dis; 30(2):121-33.	海外
—	Cavalli G, Tomelleri A, De Luca G, et al. (2019) Efficacy of canakinumab as first-line biologic agent in adult-onset Still's disease. Arthritis Res Ther; 21(1):54.	海外
—	Cota-Arce JM, Cota J, De León-Nava MA, et al. (2021) Efficacy and safety of canakinumab in the treatment of adult-onset Still's disease: A systematic review. Semin Arthritis Rheum; 51(6):1282-90.	海外
—	Dunger-Baldauf C, Nakasato P, Noviello S, et al. (2022) Similar Clinical Outcomes in Patients with Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease Treated with Canakinumab: Bayesian and Population Model-Based Analyses. Rheumatol Ther; 9(2):753-62.	海外
—	Efthimiou P and Georgy S (2006) Pathogenesis and management of adult-onset Still's disease. Semin Arthritis Rheum; 36(3):144-52.	海外

添付資料番号	著者・表 題・掲載誌	報種類（国内／海外）
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