ヌーカラ皮下注 100mg シリンジ
ヌーカラ皮下注 100mg ペン
に関する資料

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1.5. 起原又は発見の経緯及び開発の経緯

1.5.1. 本申請に至った経緯

メポリズマブ（遺伝子組換え）（以下、メポリズマブ）は、血中及び組織中の好酸球を制御する主なサイトカインであるヒトインターロイキン-5 に特異的かつ高親和性に結合するヒト化モノクローナル抗体である。

メポリズマブは、本邦において「ヌーカラ皮下注用 100 mg」の販売名で、2016 年 3 月に成人及び 12 歳以上の小児に対して「気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）」の効能・効果で承認されている。また、2018 年 5 月に成人に対して「既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症」の効能・効果で承認され、2020 年 3 月に気管支喘息について、6 歳以上 12 歳未満の小児に対する用法・用量が承認されている。

2020 年 3 月には、凍結乾燥製剤である「ヌーカラ皮下注用 100 mg」に加え、安全装置と組み合わせたメポリズマブの薬液が充填されたプレフィルドシリンジ（PFS）製剤（安全装置付き PFS 製剤）である「ヌーカラ皮下注 100 mg シリンジ」と、ペン型の注入器と組み合わせたメポリズマブの薬液が充填された PFS 製剤である「ヌーカラ皮下注 100 mg ペン」が承認されている。更に、2022 年 6 月にこれまで凍結乾燥製剤を使用する必要があった 6 歳以上 12 歳未満の小児の気管支喘息に対し、メポリズマブを 40 mg 含有する安全装置付き PFS 製剤である「小児用ヌーカラ皮下注 40 mg シリンジ」が承認されている。

今般、グラクソ・スミスクライン株式会社は、鼻茸を伴う慢性副鼻腔炎（CRSwNP）患者を対象とした国際共同試験等において、メポリズマブの有効性及び安全性が確認されたことから、2つの第III相試験（209692試験及び205687試験）と第II相試験（MPP111782試験）を評価資料として、表 1.5.1.1 に示す通り、CRSwNPの効能・効果、用法・用量の追加に係る医薬品製造販売承認事項一部変更承認申請を行うこととした。

なお、209692試験において、自己投与を行う意思がある日本人被験者は、Week 32以降に医療従事者の監督の下、自己投与を実施した。

表 1.5.1.1　申請内容

申請品目	ヌーカラ皮下注 100 mg シリンジ、ヌーカラ皮下注 100 mg ペン
申請区分	医療用医薬品（4）新効能医薬品、（6）新用量医薬品
効能・効果（案）	気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る） 既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症 鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る） （下線部追加）
用法・用量（案）	気管支喘息 通常、成人及び 12 歳以上の小児にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。 好酸球性多発血管炎性肉芽腫症 通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 300 mg を 4 週間ごとに皮下に注射する。 鼻茸を伴う慢性副鼻腔炎 通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。 （下線部追加）

起原又は発見の経緯及び開発の経緯等のうち、当該内容が第 2 部に記載できる場合には、第 2 部での当該内容の記載箇所を 表 1.5.1.2 に示し、第 1 部（5）における記載を省略する。

表 1.5.1.2　第 1 部（5）に関する内容の第 2 部における記載場所

第 1 部（5）に記載する内容	第 2 部の記載箇所
CRSwNP の疾患、診断及び治療法	2.5.1.1. 疾患について 2.5.1.2. 現在の治療法及びアンメットメディカルニーズ
臨床開発計画、本申請における臨床データパッケージ及び規制当局からの助言	2.5.1.4. 臨床開発計画
メポリズマブの有効性、安全性に基づく有用性	2.5.6. ベネフィットとリスクに関する結論

また、開発の経緯図を 図 1.5.1.1 に示す。

なお、本申請に際して、品質及び非臨床に関する新たな資料の提出はない。

試験項目/試験番号[1]		国内	海外	[redacted]
第 II 相試験	MPP111782		○	
第 III 相試験	205687		○	
第 III 相試験	209692	○	○	
特定使用成績調査（気管支喘息）	204524	○		
特定使用成績調査（好酸球性多発血管炎性肉芽腫症）	208505	○		

1. 好酸球性多発血管炎性肉芽腫症を対象とした MEA115921 試験の安全性追加解析も臨床データパッケージに含まれる。
2. データカットオフ時期

図 1.5.1.1 開発の経緯図

1.5.2. 申請製剤、申請効能以外の開発

1.5.2.1. 申請製剤以外の開発

[redacted]

1.5.2.2. 申請効能以外の開発

現在、海外において、メポリズマブに対する[redacted]の開発が進められている。

1.6. 外国における使用状況等に関する資料

メポリズマブ（遺伝子組換え）は、鼻茸を伴う慢性副鼻腔炎の適応に対し、米国及び欧州においてそれぞれ 2021 年 7 月、2021 年 11 月に承認されており、2024 年 5 月 13 日現在、50 以上の国又は地域で承認されている。

本項では、以下の資料を添付した。

- 米国における添付文書の原文
- 欧州における添付文書の原文
- 企業中核データシート（COMPANY CORE DATASHEET）の原文

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUCALA safely and effectively. See full prescribing information for NUCALA.

NUCALA (mepolizumab) for injection, for subcutaneous use
NUCALA (mepolizumab) injection, for subcutaneous use
Initial U.S. Approval: 2015

---------- INDICATIONS AND USAGE----------
NUCALA is an interleukin-5 (IL-5) antagonist monoclonal antibody (IgG1 kappa) indicated for:
- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype. (1.1)
- Add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP). (1.2)
- The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). (1.3)
- The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause. (1.4)

Limitations of use: Not for relief of acute bronchospasm or status asthmaticus. (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Severe asthma in patients aged 12 years and older: 100 mg administered subcutaneously once every 4 weeks. (2.1)
- Severe asthma in patients aged 6 to 11 years: 40 mg administered subcutaneously once every 4 weeks. (2.1)
- CRSwNP: 100 mg administered subcutaneously once every 4 weeks. (2.2)
- EGPA: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks. (2.3)
- HES: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks. (2.4)

---------- DOSAGE FORMS AND STRENGTHS----------
- For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution. (3)
- Injection: 100 mg/mL, single-dose prefilled autoinjector or single-dose prefilled syringe. (3)
- Injection: 40 mg/0.4 mL, single-dose prefilled syringe. (3)

---------- CONTRAINDICATIONS ----------
History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Discontinue NUCALA in the event of a hypersensitivity reaction. (5.1)
- Do not use to treat acute bronchospasm or status asthmaticus. (5.2)
- Herpes zoster infections have occurred in patients receiving NUCALA. Consider vaccination if medically appropriate. (5.3)
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate. (5.4)
- Treat patients with pre-existing helminth infections before therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until parasitic infection resolves. (5.5)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥5%):
- Asthma: Headache, injection site reaction, back pain, and fatigue. (6.1)
- CRSwNP: Oropharyngeal pain and arthralgia. (6.2)
- EGPA and HES: Most common adverse reactions are similar to asthma. (6.3, 6.4)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2023

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- 1.1 Maintenance Treatment of Severe Asthma
- 1.2 Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps
- 1.3 Eosinophilic Granulomatosis with Polyangiitis
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Severe Asthma

NUCALA is indicated for the add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype *[see Use in Specific Populations (8.4), Clinical Studies (14.1)]*.

Limitations of Use

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

1.2 Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

1.3 Eosinophilic Granulomatosis with Polyangiitis

NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

1.4 Hypereosinophilic Syndrome

NUCALA is indicated for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

2 DOSAGE AND ADMINISTRATION

NUCALA is for subcutaneous use only.

2.1 Severe Asthma

Adults and Adolescents Aged 12 Years and Older

The recommended dosage of NUCALA in adults and adolescents aged 12 years and older is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen *[see Dosage and Administration (2.5, 2.6)]*.

Pediatric Patients Aged 6 to 11 Years

The recommended dosage of NUCALA for injection in pediatric patients aged 6 to 11 years is 40 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen *[see Dosage and Administration (2.5, 2.6)]*.

2.2 Chronic Rhinosinusitis with Nasal Polyps

The recommended dosage of NUCALA is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen *[see Dosage and Administration (2.5, 2.6)]*.

2.3 Eosinophilic Granulomatosis with Polyangiitis

The recommended dosage of NUCALA is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen *[see Dosage and Administration (2.5, 2.6)]*. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

2.4 Hypereosinophilic Syndrome

The recommended dosage of NUCALA is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen *[see Dosage and Administration (2.5, 2.6)]*. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

2.5 Preparation and Administration of NUCALA for Injection Vial

NUCALA for injection should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1)]*.

Reconstitution Instructions

1. Reconstitute NUCALA for injection in the vial with 1.2 mL of Sterile Water for Injection, USP, preferably using a 2- or 3-mL syringe and a 21-gauge needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab. Do not mix with other medications.
2. Direct the stream of Sterile Water for Injection vertically onto the center of the lyophilized powder, which may have a cake-like appearance. Gently swirl the vial for 10 seconds with a circular motion at 15-second intervals until the powder is dissolved.

   Note: Do not shake the reconstituted solution during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the Sterile Water for Injection has been added, but it may take additional time.
3. If a mechanical reconstitution device (swirler) is used to reconstitute NUCALA for injection, swirl at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1,000 rpm for no longer than 5 minutes is acceptable.
4. Visually inspect the reconstituted solution for particulate matter and clarity before use. The solution should be clear to opalescent and colorless to pale yellow or pale brown, essentially particle free. Small air bubbles, however, are expected and acceptable. If particulate matter

remains in the solution or if the solution appears cloudy or milky, the solution must not be administered.

5. If the reconstituted solution is not used immediately:
   - store below 30°C (86°F),
   - do not freeze, and
   - discard if not used within 8 hours of reconstitution.

Administration of 100-mg Dose

1. For subcutaneous administration, preferably using a 1-mL polypropylene syringe fitted with a disposable 21- to 27-gauge x 0.5-inch (13-mm) needle.
2. Just before administration, remove 1 mL of reconstituted NUCALA for injection. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1-mL injection (equivalent to 100 mg of mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Administration of 40-mg Dose

1. For subcutaneous administration, preferably using a 1-mL polypropylene syringe fitted with a disposable 21- to 27-gauge x 0.5-inch (13-mm) needle.
2. Just before administration, remove 0.4 mL of reconstituted NUCALA for injection. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 0.4-mL injection (equivalent to 40 mg of mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Each vial of NUCALA for injection should be used for a single patient, and any remainder of the contents should be discarded.

2.6 Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringes

NUCALA injection is intended for use under the guidance of a healthcare provider.

The 100-mg/mL prefilled autoinjector and 100-mg/mL prefilled syringe are only for use in adults and adolescents aged 12 years and older. A patient may self-inject or the patient caregiver may administer NUCALA injection 100 mg/mL subcutaneously after the healthcare provider determines it is appropriate.

The 40-mg/0.4-mL prefilled syringe is only for use in children aged 6 to 11 years and must be administered by the healthcare provider or the patient caregiver. The patient caregiver may

administer NUCALA injection 40 mg/0.4 mL subcutaneously after the healthcare provider determines it is appropriate.

Provide proper training in subcutaneous injection technique and on the preparation and administration of NUCALA injection prior to use *[see Instructions for Use]*.

1. Remove the prefilled autoinjector or prefilled syringe from the refrigerator and allow it to sit at room temperature for 30 minutes prior to injection. Do not warm NUCALA injection in any other way.
2. Prior to administration, visually inspect the window of the prefilled autoinjector or the prefilled syringe for particulate matter or discoloration. NUCALA injection should be clear to opalescent, colorless to pale yellow to pale brown in color. Do not use NUCALA injection if the product exhibits discoloration, cloudiness, or particulate matter. Do not use the NUCALA prefilled autoinjector or prefilled syringe if dropped on a hard surface.
3. Administer the subcutaneous injection into the thigh or abdomen, avoiding the 5 cm (approximately 2 inches) around the navel. The upper arm can also be used if a caregiver administers the subcutaneous injection.
4. For use in EGPA and HES, ensure injection sites for each subcutaneous injection are separated by at least 5 cm (approximately 2 inches).
5. Never give injections into areas where the skin is tender, bruised, red, or hard.
6. If a dose is missed, administer a dose as soon as possible. Thereafter, the patient can resume dosing on the usual day of administration. If the next dose is already due, then administer as planned.

3 DOSAGE FORMS AND STRENGTHS

For injection

- 100 mg white to off-white lyophilized powder in a single-dose vial for reconstitution.

Injection

- 100 mg/mL as a clear to opalescent, colorless to pale yellow to pale brown solution in a single-dose prefilled autoinjector.
- 100 mg/mL as a clear to opalescent, colorless to pale yellow to pale brown solution in a single-dose prefilled glass syringe.
- 40 mg/0.4 mL as a clear to opalescent, colorless to pale yellow to pale brown solution in a single-dose prefilled glass syringe.

4 CONTRAINDICATIONS

NUCALA is contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation *[see Warnings and Precautions (5.1), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

5.3 Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions (6.1)]*. Consider vaccination if medically appropriate.

5.4 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dosage, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dosage may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.5 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*

- Opportunistic infections: herpes zoster *[see Warnings and Precautions (5.3)]*

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

6.1 Clinical Trials Experience in Severe Asthma

Adult and Adolescent Patients Aged 12 Years and Older

A total of 1,327 patients with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT01000506; Trial 2, NCT01691521; and Trial 3, NCT01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 patients required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All patients had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1)]*. Of the patients enrolled, 59% were female, 85% were White, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 patients received NUCALA (mepolizumab 100 mg subcutaneous) for at least 24 weeks. Serious adverse events that occurred in more than 1 patient and in a greater percentage of patients receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of patients receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with Severe Asthma (Trials 2 and 3)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2

Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial: Adverse reactions from Trial 1 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with ≥3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in patients receiving mepolizumab 75 mg IV compared with 2 patients in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving NUCALA 100 mg and 3% of patients in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.

Long-term Safety: Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the severe asthma trials described above.

Pediatric Patients Aged 6 to 11 Years

The safety data for NUCALA is based upon 1 open-label clinical trial that enrolled 36 patients with severe asthma aged 6 to 11 years. Patients received 40 mg (for those weighing <40 kg) or 100 mg (for those weighing ≥40 kg) of NUCALA administered subcutaneously once every 4 weeks. Patients received NUCALA for 12 weeks (initial short phase). After a treatment interruption of 8 weeks, 30 patients received NUCALA for a further 52 weeks (long phase). The adverse reaction profile for patients aged 6 to 11 years was similar to that observed in patients aged 12 years and older.

6.2 Clinical Trials Experience in Chronic Rhinosinusitis with Nasal Polyps

A total of 407 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received NUCALA 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent CRSwNP with a history of prior surgery and were on nasal corticosteroids for at least 8 weeks prior to screening *[see Clinical Studies (14.2)]*. Of the patients enrolled, 35% were female, 93% were White, and ages ranged from 18 to 82 years. Approximately 2% of patients receiving NUCALA 100 mg withdrew from study treatment due to adverse events compared with 2% of patients receiving placebo.

Table 2 summarizes adverse reactions that occurred in ≥3% of NUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

Table 2. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with CRSwNP

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Oropharyngeal pain	8	5
Arthralgia	6	2
Abdominal pain upper	3	2
Diarrhea	3	2
Pyrexia	3	2
Nasal dryness	3	<1
Rash	3	<1

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic [type I hypersensitivity] and other) reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and no patients in the placebo group. The manifestations of systemic allergic (type I hypersensitivity) reactions included urticaria, erythema, and rash and 1 of the 3 reactions occurred on the day of dosing. Other systemic reactions were reported by no patients in the group receiving NUCALA 100 mg and <1% of patients in the placebo group.

Injection Site Reactions

Injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving NUCALA 100 mg compared with <1% in patients receiving placebo.

6.3 Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 patients with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment *[see Clinical Studies (14.3)]*. Of the patients enrolled, 59% were female, 92% were White, and ages ranged from 20 to 71 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of NUCALA and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of NUCALA and 1% of patients in the placebo group. The manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving 300 mg of NUCALA included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor. Systemic non-allergic reactions were reported by 1 (1%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of systemic non-allergic reactions reported in the group receiving 300 mg of NUCALA was angioedema. Half of the systemic reactions in patients receiving 300 mg of NUCALA (2/4) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg of NUCALA compared with 13% in patients receiving placebo.

6.4 Clinical Trials Experience in Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients must have been on a stable dose of background HES therapy for the 4 weeks prior to randomization *[see Clinical Studies (14.4)]*. Of the patients enrolled, 53% were female, 93% were White, and ages ranged from 12 to 82 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the trial, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 (2%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of other systemic reaction was multifocal skin reaction experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

6.5 Immunogenicity

In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known. In the clinical trial of children aged 6 to 11 years with severe asthma receiving NUCALA 40 or 100 mg, 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the trial. No children had detectable anti-mepolizumab antibodies during the long phase of the trial.

In patients with CRSwNP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with CRSwNP.

In patients with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with EGPA.

In adult and adolescent patients with HES receiving 300 mg of NUCALA, 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

6.6 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval use of NUCALA. Because these reactions are reported

voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

7 DRUG INTERACTIONS

Formal drug interaction trials have not been performed with NUCALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg subcutaneous *(see Data)*.

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

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in

cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

8.4 Pediatric Use

Severe Asthma

The safety and effectiveness of NUCALA for severe asthma, and with an eosinophilic phenotype, have been established in pediatric patients aged 6 years and older.

Use of NUCALA in adolescents aged 12 to 17 years is supported by evidence from adequate and well-controlled trials in adults and adolescents. A total of 28 adolescents aged 12 to 17 years with severe asthma were enrolled in the Phase 3 asthma trials. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2, NCT01691521) and had a mean age of 14.8 years. Patients had a history of 2 or more exacerbations in the previous year despite regular use of medium- or high-dose ICS plus additional controller(s) with or without OCS and had blood eosinophils of ≥150 cells/mcL at screening or ≥300 cells/mcL within 12 months prior to enrollment. *[See Clinical Studies (14.1).]* Patients had a reduction in the rate of exacerbations that trended in favor of NUCALA. Of the 19 adolescents who received NUCALA, 9 received 100 mg and the mean apparent clearance in these patients was 35% less than that of adults. The safety profile observed in adolescents was generally similar to that of the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.

Use of NUCALA in pediatric patients aged 6 to 11 years with severe asthma, and with an eosinophilic phenotype, is supported by evidence from adequate and well-controlled trials in adults and adolescents with additional pharmacokinetic, pharmacodynamic, and safety data in

children aged 6 to 11 years. A single open-label clinical trial (NCT02377427) was conducted in 36 children aged 6 to 11 years (mean age: 8.6 years, 31% female) with severe asthma. Enrollment criteria were the same as for adolescents in the 32-week exacerbation trial (Trial 2). Based upon the pharmacokinetic data from this trial, a dose of 40 mg subcutaneous every 4 weeks was determined to have similar exposure to adults and adolescents administered a dose of 100 mg subcutaneous *[*see *Clinical Pharmacology (12.3)]*.

The effectiveness of NUCALA in pediatric patients aged 6 to 11 years is extrapolated from efficacy in adults and adolescents with support from pharmacokinetic analyses showing similar drug exposure levels for 40 mg administered subcutaneously every 4 weeks in children aged 6 to 11 years compared with adults and adolescents *[*see *Clinical Pharmacology (12.3)]*. The safety profile and pharmacodynamic response observed in this trial for children aged 6 to 11 years were similar to that seen in adults and adolescents *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.

Chronic Rhinosinusitis with Nasal Polyps

The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established.

Eosinophilic Granulomatosis with Polyangiitis

The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.

Hypereosinophilic Syndrome

The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older. The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established.

Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT02836496) in adults and adolescents and an open-label extension study (NCT03306043). One adolescent received NUCALA during the controlled study and this patient and an additional 3 adolescents received NUCALA during the open-label extension study *[see Clinical Studies (14.4)]*. The 1 adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

8.5 Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of patients aged 65 years and older that received NUCALA (n = 79) to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses

between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

10 OVERDOSAGE

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

11 DESCRIPTION

Mepolizumab is a humanized IL-5 antagonist monoclonal antibody. Mepolizumab is produced by recombinant DNA technology in Chinese hamster ovary cells. Mepolizumab has a molecular weight of approximately 149 kDa.

NUCALA for injection is a sterile, preservative-free, white to off-white, lyophilized powder in a single-dose vial for subcutaneous injection after reconstitution. Upon reconstitution with 1.2 mL of Sterile Water for Injection, USP, the resulting concentration is 100 mg/mL and delivers 1 mL *[see Dosage and Administration (2.5)]*. Each vial delivers 100 mg of mepolizumab, polysorbate 80 (0.67 mg), sodium phosphate dibasic heptahydrate (7.14 mg), and sucrose (160 mg), with a pH of 7.0.

The vial stopper is not made with natural rubber latex.

NUCALA injection is a sterile, preservative-free, clear to opalescent, colorless to pale yellow to pale brown solution for subcutaneous use.

NUCALA injection is supplied in a single-dose, 1-mL, prefilled autoinjector with a fixed 29-gauge, half-inch needle and in a single-dose, 1-mL, prefilled syringe with a fixed 29-gauge, half-inch needle with a needle guard. Each 1 mL delivers 100 mg mepolizumab, citric acid monohydrate (0.95 mg), EDTA disodium dihydrate (0.019 mg), polysorbate 80 (0.20 mg), sodium phosphate dibasic heptahydrate (4.16 mg), and sucrose (120 mg), with a pH of 6.3.

NUCALA injection is supplied in a single-dose, 0.4-mL, prefilled syringe with a fixed 29-gauge, half-inch needle with a needle guard. Each 0.4 mL delivers 40 mg mepolizumab, citric acid monohydrate (0.38 mg), EDTA disodium dihydrate (0.0074 mg), polysorbate 80 (0.08 mg), sodium phosphate dibasic heptahydrate (1.66 mg), and sucrose (48 mg), with a pH of 6.3.

The prefilled autoinjector and prefilled syringe are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mepolizumab is an IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma, CRSwNP, EGPA, and HES has not been definitively established.

12.2 Pharmacodynamics

The pharmacodynamic response (blood eosinophil reduction) following repeat doses of mepolizumab administered subcutaneously or intravenously was evaluated in adult subjects with asthma and blood eosinophil levels >200 cells/mcL. Subjects received 1 of 4 mepolizumab treatments (administered every 28 days for a total of 3 doses): 12.5 mg subcutaneous, 125 mg subcutaneous, 250 mg subcutaneous, or 75 mg IV. Sixty-six of the 70 randomized subjects completed the trial. Compared with baseline levels, blood eosinophils decreased in a dose-dependent manner. A reduction in blood eosinophil levels was observed in all treatment groups by Day 3 (48 hours post-dose). On Day 84 (4 weeks post-last dose), the observed geometric mean reduction from baseline in blood eosinophils was 64%, 78%, 84%, and 90% in the 12.5-mg subcutaneous, 75-mg IV, 125-mg subcutaneous, and 250-mg subcutaneous treatment groups, respectively. The model-predicted subcutaneous doses providing 50% and 90% of maximal reduction of blood eosinophils at Day 84 were estimated to be 11 and 99 mg, respectively. These results, along with the clinical efficacy data from the dose-ranging exacerbation trial in adult and adolescent subjects with severe asthma (Trial 1) supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the confirmatory severe asthma trials *[see Clinical Studies (14.1)]*. Following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 32 weeks in adult and adolescent subjects with severe asthma (Trial 2), blood eosinophils were reduced to a geometric mean count of 40 cells/mcL, which corresponds to a geometric mean reduction of 84% compared with placebo.

The pharmacodynamic response (blood eosinophil reduction) was also evaluated in children aged 6 to 11 years with severe asthma. Following subcutaneous administration of mepolizumab 40 mg every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 48 cells/mcL. This corresponds to a geometric mean reduction from baseline of 85%.

The magnitude of reduction in adults, adolescents, and children was observed within 4 weeks of treatment and was maintained throughout the treatment periods.

For adults with CRSwNP, following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 60 cells/mcL. There was a geometric mean reduction of 83% compared with placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period *[see Clinical Studies (14.2)]*.

For adults with EGPA, following subcutaneous administration of mepolizumab 300 mg every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 38 cells/mcL. There was a geometric mean reduction of 83% compared with placebo, and this magnitude of reduction was observed within 4 weeks of treatment *[see Clinical Studies (14.3)]*.

For adults and adolescents with HES, following subcutaneous administration of mepolizumab 300 mg every 4 weeks for 32 weeks, blood eosinophils were reduced to a geometric mean count of 70 cells/mcL. There was a geometric mean reduction of 92% compared with placebo *[see Clinical Studies (14.4)]*.

12.3 Pharmacokinetics

Following subcutaneous dosing in adult subjects with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 to 250 mg. The pharmacokinetic properties of mepolizumab observed in subjects with CRSwNP (adults), EGPA (adults), or HES (adults and adolescents) were similar to the pharmacokinetic properties observed in subjects with severe asthma (adults and adolescents).

Subcutaneous administration of mepolizumab 300 mg had approximately 3 times the systemic exposure of mepolizumab 100 mg.

Absorption

Following 100-mg subcutaneous administration in the upper arm of adult and adolescent subjects with asthma, the bioavailability of mepolizumab was estimated to be approximately 80%.

Following repeat subcutaneous administration once every 4 weeks, there was approximately a 2-fold accumulation at steady state.

Distribution

The population central volume of distribution of mepolizumab in adult subjects with asthma is estimated to be 3.6 L for a 70-kg individual.

Elimination

Following subcutaneous administration of mepolizumab in adult subjects with asthma, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. The population apparent systemic clearance of mepolizumab in adult and adolescent subjects with asthma is estimated to be 0.28 L/day for a 70-kg individual.

Metabolism: Mepolizumab is a humanized IgG1 monoclonal antibody that is degraded by the proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue.

Specific Populations

Racial Groups and Male and Female Patients: Population pharmacokinetics analyses indicated there was no significant effect of race and gender on mepolizumab clearance.

Age: Population pharmacokinetics analyses indicated there was no significant effect of age on mepolizumab clearance.

Pediatric Patients: Mepolizumab pharmacokinetics following subcutaneous administration in subjects aged 6 to 11 years with severe asthma was investigated in the initial 12-week treatment phase of an open-label clinical trial. Exposures (AUC) following subcutaneous administration of either 40 mg (for children weighing <40 kg) or 100 mg (for children weighing ≥40 kg) were 1.32 and 1.97 times higher, respectively, compared with that observed in adults and adolescents receiving 100 mg. Based on these results, simulation of a 40-mg subcutaneous dose every 4 weeks in children aged 6 to 11 years, irrespective of body weight, resulted in predicted exposures similar to that observed in adults and adolescents.

Patients with Renal Impairment: No clinical trials have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, mepolizumab clearance was comparable between subjects with creatinine clearance values between 50 and 80 mL/min and patients with normal renal function. There are limited data available in subjects with creatinine clearance values <50 mL/min; however, mepolizumab is not cleared renally.

Patients with Hepatic Impairment: No clinical trials have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Drug Interaction Studies

No formal drug interaction studies have been conducted with mepolizumab. In population pharmacokinetics analyses of Phase 3 studies, there was no evidence of an effect of commonly coadministered small molecule drugs on mepolizumab exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote

tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week.

14 CLINICAL STUDIES

14.1 Severe Asthma

The asthma development program for NUCALA in patients aged 12 years and older included 3 double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial (Trial 1, NCT01000506) and 2 confirmatory trials (Trial 2, NCT01691521 and Trial 3, NCT01691508). Mepolizumab was administered every 4 weeks in all 3 trials as add-on to background treatment. All patients continued their background asthma therapy throughout the duration of the trials.

Dose-Ranging and Exacerbation Trial

Trial 1 was a 52-week dose-ranging and exacerbation-reduction trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients enrolled in this trial were required to have at least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count ≥300 cells/mcL, sputum eosinophil count ≥3%, exhaled nitric oxide concentration ≥50 ppb, or deterioration of asthma control after ≤25% reduction in regular maintenance ICS/OCS. Three IV dosages of mepolizumab (75, 250, and 750 mg) administered once every 4 weeks were evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the subsequent trials *[see Clinical Pharmacology (12.2)]*. NUCALA is not indicated for IV use and should only be administered by the subcutaneous route.

Confirmatory Trials

A total of 711 patients with severe asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials patients were required to have blood eosinophils of ≥150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of ≥300 cells/mcL within 12 months of enrollment. The screening blood eosinophils of ≥150 cells/mcL criterion was derived from exploratory analyses of data from Trial 1. Trial 2 was a 32-week placebo- and active-controlled trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients

received mepolizumab 75 mg IV (n = 191), NUCALA 100 mg (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks.

Trial 3 was a 24-week OCS-reduction trial in patients with severe asthma who required daily OCS in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control. Patients in Trial 3 were not required to have a history of exacerbations in the previous year. Patients received NUCALA 100 mg (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. The baseline mean OCS use was similar in the 2 treatment groups: 13.2 mg in the placebo group and 12.4 mg in the group receiving NUCALA 100 mg.

The demographics and baseline characteristics of these 3 trials are provided in Table 3.

Table 3. Demographics and Baseline Characteristics of Severe Asthma Trials

	Trial 1 (N = 616)	**Trial 2 (N = 576)**	**Trial 3 (N = 135)**
Mean age, years	49	50	50
Female, n (%)	387 (63)	328 (57)	74 (55)
White, n (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, years, mean	19	20	19
Never smoked, n (%)	483 (78)	417 (72)	82 (61)
Baseline FEV_1, L	1.88	1.82	1.95
Baseline % predicted FEV_1	60	61	59
Baseline % reversibility	25	27	26
Baseline post-SABA FEV_1/FVC	0.67	0.66	0.66
Geometric mean eosinophil count at baseline, cells/mcL	250	290	240
Mean number of exacerbations in previous year	3.6	3.6	3.1

FEV_1 = forced expiratory volume in 1 second, SABA = short-acting $beta_2$-agonist, FVC = forced vital capacity.

Exacerbations

Efficacy was assessed in Trials 1 and 2 using an endpoint of the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For patients on maintenance OCS, an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days. Compared with placebo, patients receiving NUCALA 100 mg or mepolizumab 75 mg IV experienced significantly fewer exacerbations. Additionally, compared with placebo, there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with NUCALA 100 mg (Table 4).

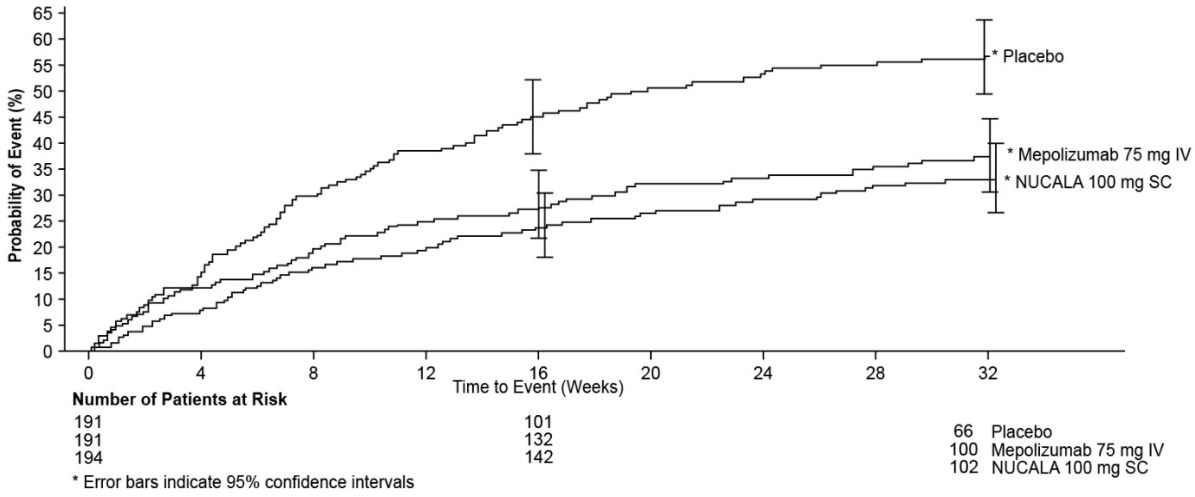
Table 4. Rate of Exacerbations in Severe Asthma Trials 1 and 2 (Intent-to-Treat Population)

Trial	Treatment	Exacerbations per Year		
		Rate	Difference	Rate Ratio (95% CI)
All exacerbations				
Trial 1	Placebo (n = 155)	2.40		
	Mepolizumab 75 mg IV (n = 153)	1.24	1.16	0.52 (0.39, 0.69)
Trial 2	Placebo (n = 191)	1.74		
	Mepolizumab 75 mg IV (n = 191)	0.93	0.81	0.53 (0.40, 0.72)
	NUCALA 100 mg SC (n = 194)	0.83	0.91	0.47 (0.35, 0.64)
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	Placebo (n = 155)	0.43		
	Mepolizumab 75 mg IV (n = 153)	0.17	0.26	0.40 (0.19, 0.81)
Trial 2	Placebo (n = 191)	0.20		
	Mepolizumab 75 mg IV (n = 191)	0.14	0.06	0.68 (0.33, 1.41)
	NUCALA 100 mg SC (n = 194)	0.08	0.12	0.39 (0.18, 0.83)
Exacerbations requiring hospitalization				
Trial 1	Placebo (n = 155)	0.18		
	Mepolizumab 75 mg IV (n = 153)	0.11	0.07	0.61 (0.28, 1.33)
Trial 2	Placebo (n = 191)	0.10		
	Mepolizumab 75 mg IV (n = 191)	0.06	0.04	0.61 (0.23, 1.66)
	NUCALA 100 mg SC (n = 194)	0.03	0.07	0.31 (0.11, 0.91)

IV = intravenous, SC = subcutaneous.

The time to first exacerbation was longer for the groups receiving NUCALA 100 mg and mepolizumab 75 mg IV compared with placebo in Trial 2 (Figure 1).

Figure 1. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Severe Asthma Trial 2)



IV = intravenous, SC = subcutaneous.

Trial 1 data were explored to determine criteria that could identify patients likely to benefit from treatment with NUCALA. The exploratory analysis suggested that baseline blood eosinophil count of ≥150 cells/mcL was a potential predictor of treatment benefit. Exploratory analysis of Trial 2 data also suggested that baseline blood eosinophil count (obtained within 6 weeks of initiation of dosing) of ≥150 cells/mcL was a potential predictor of efficacy and showed a trend of greater exacerbation benefit with increasing blood eosinophil count. In Trial 2, patients enrolled solely on the basis of the historical blood eosinophil count of ≥300 cells/mcL in the previous 12 months, but who had a baseline blood eosinophil count <150 cells/mcL, had virtually no exacerbation benefit following treatment with NUCALA 100 mg compared with placebo.

The Asthma Control Questionnaire-5 (ACQ-5) was assessed in Trials 1 and 2, and the St. George's Respiratory Questionnaire (SGRQ) was assessed in Trial 2. In Trial 1, the ACQ-5 responder rate (defined as a decrease in score of 0.5 or more as threshold) for the 75-mg IV mepolizumab arm was 47% compared with 50% for placebo with an odds ratio (OR) of 1.1 (95% CI: 0.7, 1.7). In Trial 2, the ACQ-5 responder rate for the treatment arm for NUCALA 100 mg was 57% compared with 45% for placebo with an OR of 1.8 (95% CI: 1.2, 2.8). In Trial 2, the SGRQ responder rate (defined as a decrease in score of 4 or more as threshold) for the treatment arm for NUCALA 100 mg was 71% compared with 55% for placebo with an OR of 2.1 (95% CI: 1.3, 3.2).

Oral Corticosteroid Reduction

Trial 3 evaluated the effect of NUCALA 100 mg on reducing the use of maintenance OCS. Efficacy was assessed using an endpoint of the percent reduction of OCS dose during Weeks 20

to 24 compared with baseline dose, while maintaining asthma control. Patients were classified according to their change in OCS use during the trial with the following categories: 90% to 100% decrease, 75% to <90% decrease, 50% to <75% decrease, >0% to <50% decrease, and no improvement (i.e., no change or any increase or lack of asthma control or withdrawal of treatment). Compared with placebo, patients receiving NUCALA 100 mg achieved greater reductions in daily maintenance OCS dose, while maintaining asthma control. Sixteen (23%) patients in the group receiving NUCALA 100 mg versus 7 (11%) in the placebo group had a 90% to 100% reduction in their OCS dose. Twenty-five (36%) patients in the group receiving NUCALA 100 mg versus 37 (56%) in the placebo group were classified as having no improvement for OCS dose. Additionally, 54% of patients receiving NUCALA 100 mg achieved at least a 50% reduction in the daily prednisone dose compared with 33% of patients receiving placebo (95% CI for difference: 4%, 37%). An exploratory analysis was also performed on the subgroup of 29 patients in Trial 3 who had an average baseline and screening blood eosinophil count <150 cells/mcL. Five (29%) patients in the group receiving NUCALA 100 mg versus 0 (0%) in the placebo group had a 90% to 100% reduction in their dose. Four (24%) patients in the group receiving NUCALA 100 mg versus 8 (67%) in the placebo group were classified as having no improvement for OCS dose. The ACQ and SGRQ were also assessed in Trial 3 and showed results similar to those in Trial 2.

Lung Function

Change from baseline in mean forced expiratory volume in 1 second (FEV_1) was measured in all 3 trials and is presented in Table 5. Compared with placebo, NUCALA 100 mg did not provide consistent improvements in mean change from baseline in FEV_1.

Table 5. Change from Baseline in FEV_1 (mL) in Severe Asthma Trials

	Difference from Placebo in Mean Change from Baseline FEV_1 (mL) (95% CI)		
Trial	**Week 12**	**Week 24**	**Weeks 32/52**
1[a]	10 (-87, 108)	5 (-98, 108)	61 (-39, 161)[b]
2[c]	52 (-30, 134)	76 (-6, 159)	98 (11, 184)[d]
3[c]	56 (-91, 203)	114 (-42, 271)	NA

FEV_1 = forced expiratory volume in 1 second.

[a] Dose = 75 mg intravenous.

[b] Forced expiratory volume in 1 second (FEV_1) at Week 52.

[c] Dose = 100 mg subcutaneous.

[d] FEV_1 at Week 32.

The effect of mepolizumab on lung function was also studied in a 12-week placebo-controlled trial enrolling patients with asthma on a moderate dose of ICS with evidence of symptoms and lung function impairment. Enrollment was not dependent on a history of exacerbations or a pre-specified eosinophil count. Change from baseline in FEV_1 at Week 12 was numerically lower in the mepolizumab treatment groups than the placebo group.

14.2 Chronic Rhinosinusitis with Nasal Polyps

A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial (NCT03085797). Patients received NUCALA 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for ≥8 weeks pre-screening. Patients had recurrent and symptomatic CRSwNP, and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥5 out of 8 with NPS ≥2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0 to 10 point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 2 = polyps reaching below the lower border of the middle turbinate, 3 = large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8. Sinus CT scans were not performed at baseline nor during treatment to evaluate for sinus opacification.

The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial. Other secondary endpoints were change from baseline in loss of smell VAS score during Weeks 49 to 52, and proportion of patients requiring systemic steroids for nasal polyps up to Week 52. All VAS scores were collected daily by the patients and reported on a 0 to 10 scale (0 = none, 10 = as bad as you can imagine).

The demographics and baseline characteristics of patients in this trial are provided in Table 6.

Table 6. Demographics and Baseline Characteristics in CRSwNP

	N = 407
Mean age, years	49
Female, n (%)	143 (35)
White, n (%)	379 (93)
Mean CRSwNP duration in years (SD)	11.4 (8.4)
Patients with ≥1 surgery in past 10 years (%)	407 (100)
Patients with ≥3 surgeries in past 10 years (%)	124 (30)
OCS use (≥1 course) in past 12 months, n (%)	197 (48)
Mean bilateral endoscopic NPS[a], (SD), range 0-8	5.5 (1.29)

Mean nasal obstruction VAS score, (SD), range 0-10	9.0 (0.83)
Geometric mean blood eosinophil cells/mcL (95% CI)	390 (360, 420)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, OCS = oral corticosteroid, NPS = nasal polyp score, VAS = visual analog scale, AERD = aspirin-exacerbated respiratory disease.

[a] As graded by independent blinded assessors.

Endoscopic Nasal Polyp Score and Nasal Obstruction Visual Analog Scale Scores

Patients who received NUCALA 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52 week treatment period (Table 7).

Table 7. Analyses of Endpoints in CRSwNP

	Placebo n = 201		**NUCALA 100 mg n = 206**		
Scores[a] (range)	**Baseline Mean (SD)**	**Mean Change[b] (SE)**	**Baseline Mean (SD)**	**Mean Change[b] (SE)**	**Mean Difference vs. Placebo (95% CI)**
NPS (0-8)	5.6 (1.41)	0.06 (0.14)	5.4 (1.17)	-0.87 (0.14)	-0.93 (-1.31, -0.55)
Nasal obstruction (0-10)	9.02 (0.83)	-2.54 (0.25)	8.92 (0.83)	-4.40 (0.25)	-1.86 (-2.53, -1.19)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, SE = standard error, NPS = nasal polyp score at Week 52.

[a] Patients with nasal surgery were assigned worst possible score for the period after nasal surgery. Missing data were imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.

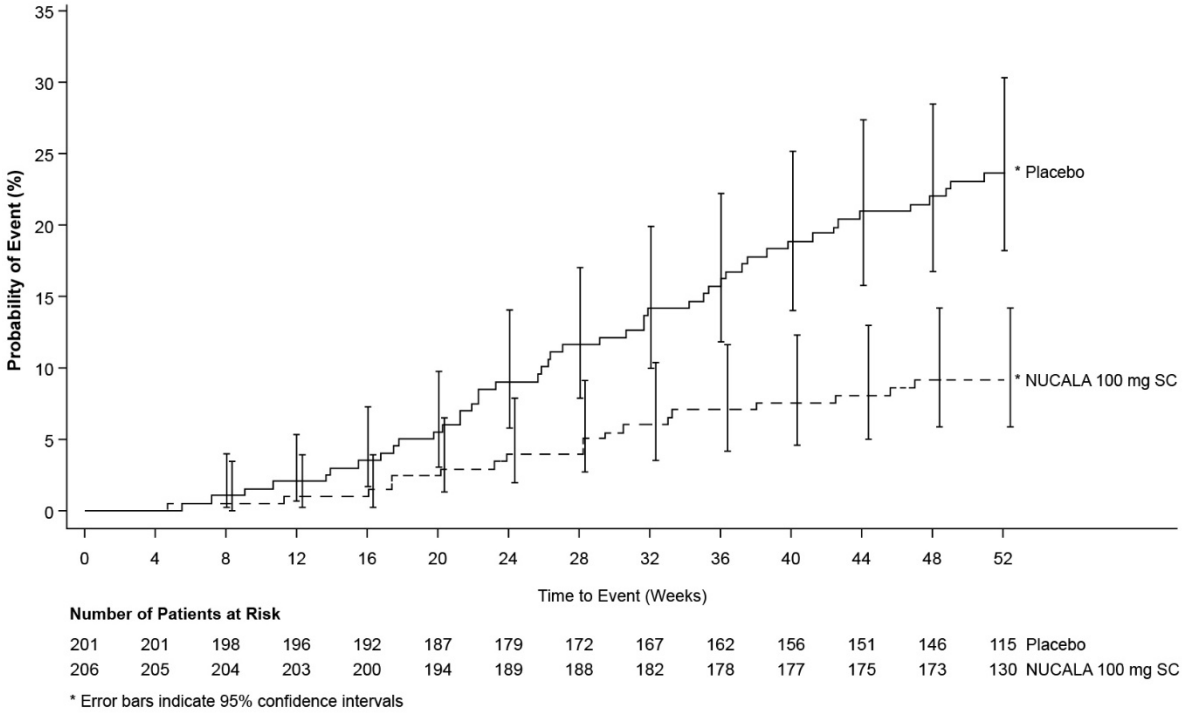
[b] Least square means from analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count, visit, interaction terms for visit by baseline and visit by treatment.

Nasal Polypectomy

The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52. The proportion of patients who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with NUCALA 100 mg compared with the

placebo group (Figure 2). By Week 52, 18 (9%) patients who received NUCALA 100 mg had surgery compared with 46 (23%) patients in the placebo group.

Figure 2. Kaplan-Meier Plot of Time to First Nasal Surgery in CRSwNP



CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SC = subcutaneous.

Additional CRSwNP Symptoms Scores

For patients who received NUCALA 100 mg, statistically significant improvement was observed in loss of smell compared to placebo and improvements were also observed in the individual VAS symptom scores compared with patients in the placebo group in the 4-weeks prior to the end of the 52-week treatment period (Table 8).

Table 8: Additional Visual Analog Scale Symptom Scores Assessed at Weeks 49-52

VAS Scores[a] (range)	Placebo n = 201		NUCALA 100 mg n = 206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)	Mean Change[b] (SE)	Baseline Mean (SD)	Mean Change[b] (SE)	
Loss of smell (0-10)	9.68 (0.60)	-1.46 (0.24)	9.63 (0.83)	-2.92 (0.24)	-1.46 (-2.11, -0.81)
Nasal discharge[c] (0-10)	8.78 (1.25)	-2.49 (0.26)	8.78 (1.07)	-4.38 (0.25)	-1.89 (-2.58, -1.20)
Mucus in the throat[c] (0-10)	8.58 (1.63)	-2.37 (0.26)	8.51 (1.61)	-4.07 (0.26)	-1.70 (-2.41, -0.99)
Facial pain[c] (0-10)	7.77 (2.72)	-2.04 (0.28)	7.76 (2.51)	-3.73 (0.27)	-1.69 (-2.43, -0.95)

VAS = visual analog scale; SD = standard deviation; SE = standard error.

[a] Patients with nasal surgery were assigned the worst possible score for the period after nasal surgery. Missing data was imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.

[b] Least square means from an analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count visit, interaction terms for visit by baseline and visit by treatment.

[c] This endpoint was not prespecified in the analysis plan to adjust for multiplicity.

Corticosteroid Reduction

Treatment with NUCALA 100 mg significantly reduced the need for systemic steroids for nasal polyps vs. placebo up to Week 52 (odds ratio: 0.58, 95% CI: 0.36, 0.92). In patients who received NUCALA 100 mg, 52 (25%) required ≥1 course of systemic steroids compared with 74 (37%) in the placebo group throughout the 52-week treatment period.

Results in Patients with Co-morbid Asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received NUCALA 100 mg compared with placebo. Additionally, based on a post-hoc analysis in these patients, there was a greater response from baseline at Week 52 in asthma control as measured by the ACQ-5 for NUCALA 100 mg compared with placebo (57% of the NUCALA patients met the responder threshold reduction of ≥0.5, compared to 35% in the placebo group, with an odds ratio of 2.42 [95% CI 1.43, 4.11]).

14.3 Eosinophilic Granulomatosis with Polyangiitis

A total of 136 adult patients with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT02020889). Patients received 300 mg of NUCALA or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. Efficacy was assessed in this trial using co-endpoints of the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of patients in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.

The demographics and baseline characteristics of patients in this trial are provided in Table 9.

Table 9. Demographics and Baseline Characteristics in EGPA

	N = 136
Mean age, years	48.5
Female, n (%)	80 (59)
White, n (%)	125 (92)
Duration of EGPA, years, mean (SD)	5.5 (4.63)
History of ≥1 confirmed relapse in past 2 years, n (%)	100 (74)
Refractory disease, n (%) Recurrence of EGPA symptoms, n (%) Failed induction treatment, n (%)	74 (54) 68 (50) 6 (4)
Baseline oral corticosteroid[a] daily dose, mg, median (range)	12 (7.5-50)
Receiving immunosuppressive therapy[b], n (%)	72 (53)

EGPA = Eosinophilic Granulomatosis with Polyangiitis, SD = standard deviation.

[a] Prednisone or prednisolone equivalent.

[b] e.g., azathioprine, methotrexate, mycophenolic acid.

Remission

Patients receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of patients receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (Table 10). Results of the components of remission are also shown in Table 10. In addition, significantly more patients receiving 300 mg of NUCALA achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week trial treatment period compared with placebo (19% for 300 mg of NUCALA versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

Table 10. Remission and Components of Remission in EGPA

	Remission (OCS ≤4 mg/day + BVAS = 0)		OCS ≤4 mg/day		BVAS = 0	
	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68
Accrued duration over 52 weeks, n (%)						
0	55 (81)	32 (47)	46 (68)	27 (40)	6 (9)	3 (4)
>0 to <12 weeks	8 (12)	8 (12)	12 (18)	5 (7)	15 (22)	13 (19)
12 to <24 weeks	3 (4)	9 (13)	6 (9)	12 (18)	11 (16)	5 (7)
24 to <36 weeks	0	10 (15)	2 (3)	10 (15)	17 (25)	2 (3)
≥36 weeks	2 (3)	9 (13)	2 (3)	14 (21)	19 (28)	45 (66)
Odds ratio (NUCALA/placebo)[a] (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of patients at both Weeks 36 and 48						
Patients, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (NUCALA/placebo)[a] (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

EGPA = Eosinophilic Granulomatosis with Polyangiitis, OCS = oral corticosteroid, BVAS = Birmingham Vasculitis Activity Score.

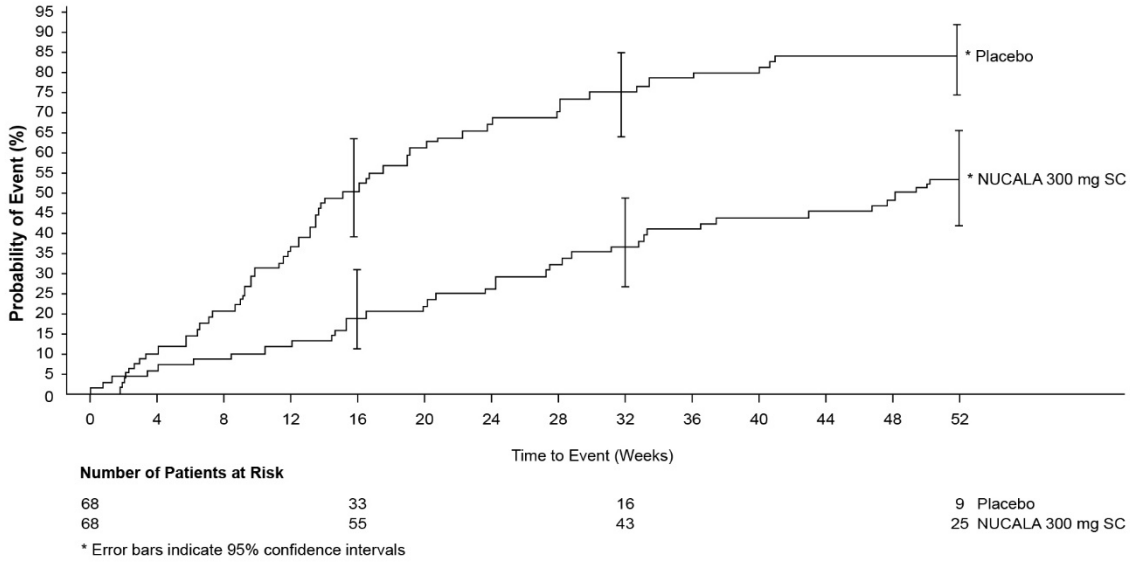
[a] An odds ratio >1 favors NUCALA.

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day.

Relapse

The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for patients receiving 300 mg of NUCALA compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 3). Additionally, patients receiving 300 mg of NUCALA had a reduction in rate of relapse compared with patients receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for 300 mg of NUCALA compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with NUCALA compared with placebo.

Figure 3. Kaplan-Meier Plot of Time to First Relapse in EGPA



EGPA = Eosinophilic Granulomatosis with Polyangiitis, SC = subcutaneous.

Corticosteroid Reduction

Patients receiving 300 mg of NUCALA had a significantly greater reduction in average daily OCS dose compared with patients receiving placebo during Weeks 48 to 52 (Table 11).

Table 11. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of Patients	
	Placebo n = 68	**NUCALA 300 mg n = 68**
0	2 (3)	12 (18)
>0 to ≤4.0 mg	3 (4)	18 (26)
>4.0 to ≤7.5 mg	18 (26)	10 (15)
>7.5 mg	45 (66)	28 (41)
Comparison: NUCALA/placebo[a]		
Odds ratio[b]		0.20
95% CI		0.09, 0.41

EGPA = Eosinophilic Granulomatosis with Polyangiitis.

[a] Analyzed using a proportional odds model with covariates of treatment group, baseline oral corticosteroid daily dose, baseline Birmingham Vasculitis Activity Score, and region.

[b] An odds ratio <1 favors NUCALA.

Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the patient, was developed to measure the adequacy of asthma control and change in asthma control. The on-treatment ACQ-6 responder rate during Weeks 48 to 52 (defined as a decrease in score of 0.5 or more compared with baseline) was 22% for 300 mg of NUCALA and 16% for placebo (OR 1.56; 95% CI: 0.63, 3.88 for 300 mg of NUCALA compared with placebo).

14.4 Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES for at least 6 months were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial (NCT02836496). Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks while continuing their stable HES therapy. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and a blood eosinophil count of 1,000 cells/mcL or higher during screening. Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy could include chronic or episodic OCS, immunosuppressive, or cytotoxic therapy.

The efficacy of NUCALA in HES was established based upon the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy.

The demographics and baseline characteristics of patients in this trial are provided in Table 12.

Table 12. Demographics and Baseline Characteristics in HES

	N = 108
Mean age, years (SD)	46.0 (15.78)
Female, n (%)	57 (53)
White, n (%)	100 (93)
Mean duration of HES, years	5.55

HES = Hypereosinophilic Syndrome, SD = standard deviation.

Flares

The trial compared the proportion of patients who experienced a HES flare or withdrew from the trial in the NUCALA and placebo treatment groups (Table 13). Over the 32-week treatment

period, the incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with NUCALA (50% reduction).

Table 13. Overview of HES Flares

	Number (%) of Patients	
	Placebo n = 54	**NUCALA 300 mg n = 54**
Patients with ≥1 HES flare or who withdrew from trial	30 (56)	15 (28)
Patients with ≥1 HES flare	28 (52)	14 (26)
Patients with no HES flare who withdrew from trial	2 (4)	1 (2)
Comparison: NUCALA/placebo[a]		
CMH *P* value		0.002
Odds ratio[b]		0.28
95% CI		(0.12, 0.64)

HES = Hypereosinophilic Syndrome, CMH = Cochran-Mantel-Haenszel.

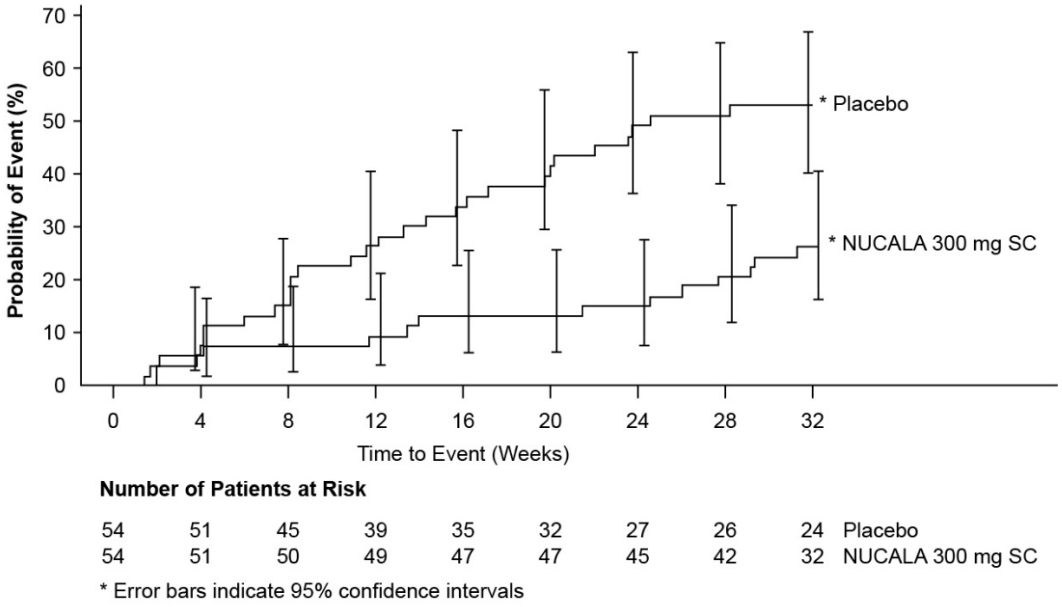
[a] Analysis compared the number of patients who experienced ≥1 HES flare and/or withdrew from the trial prematurely.

[b] An odds ratio <1 favors NUCALA.

Time to First Flare

Difference was observed between NUCALA and placebo arms in the time to first HES flare (Figure 4). The risk of first HES flare over the treatment period was 66 % lower for patients treated with NUCALA compared with placebo (hazard ratio: 0.34; 95 % CI 0.18, 0.67, $P = 0.002$).

Figure 4. Kaplan-Meier Curve for Time to First HES Flare



HES = Hypereosinophilic Syndrome, SC = subcutaneous.

Proportion of Patients Who Experienced Flares during Week 20 through Week 32

From Week 20 through Week 32, significantly fewer patients experienced a HES flare or withdrew from the trial when treated with 300 mg of NUCALA compared with placebo (17% vs. 35%, respectively, $P = 0.020$; OR: 0.33; 95 % CI: 0.13, 0.85).

Rate of Flares

Patients who received NUCALA experienced significantly fewer HES flares during the 32-week treatment period compared with the placebo group (Table 14). Treatment with NUCALA resulted in a statistically significant 66% reduction in the annualized rate of HES flares compared with placebo.

Table 14. Frequency of Flares

	Number (%) of Patients	
	Placebo n = 54	**NUCALA 300 mg n = 54**
0	26 (48)	40 (74)
1	15 (28)	11 (20)
2	7 (13)	3 (6)
3	5 (9)	0
4	1 (2)	0
≥5	0	0
Comparison: NUCALA/placebo		
Wilcoxon *P* value (unadjusted/adjusted)[a]		0.002/0.02
Rate/year	1.46	0.50
Rate ratio[b]		0.34
95% CI		(0.19, 0.63)

[a] Adjusted *P* values based on pre-specified hierarchy of endpoints.
[b] A rate ratio <1 favors NUCALA.

Brief Fatigue Inventory

Brief Fatigue Inventory (BFI) Item 3 asks patients to record their worst level of weariness/tiredness severity during the past 24 hours (scale: 0 = no fatigue to 10 = as bad as you can imagine). At baseline, median BFI Item 3 scores were similar between treatment groups (4.46 for NUCALA 300 mg and 4.69 for placebo). At Week 32, BFI Item 3 scores improved with NUCALA compared with placebo ($P = 0.036$). The median change from baseline score for BFI Item 3 at Week 32 was -0.66 in the group treated with NUCALA and 0.32 in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUCALA for Injection

NUCALA (mepolizumab) for injection is a sterile, preservative-free, white to off-white, lyophilized powder for reconstitution and subcutaneous injection in a single-dose glass vial with a flip-off seal. The vial stopper is not made with natural rubber latex.

NUCALA for injection is supplied as:
100-mg single-dose vials in cartons of 1 (NDC 0173-0881-01).

Store vials below 77°F (25°C). Do not freeze. Store in the original carton to protect from light.

NUCALA Injection

NUCALA (mepolizumab) injection is a sterile, preservative-free, clear to opalescent, colorless to pale yellow to pale brown solution for subcutaneous use. Each single-dose prefilled autoinjector delivers 100 mg of mepolizumab in 1 mL of solution. Each single-dose prefilled syringe delivers 100 mg of mepolizumab in 1 mL of solution or 40 mg of mepolizumab in 0.4 mL of solution. The autoinjectors and syringes are not made with natural rubber latex.

NUCALA injection is supplied as:

- 100 mg/mL, single-dose, prefilled autoinjector with attached 29-gauge, half-inch needle in cartons of 1 (NDC 0173-0892-01).
- 100 mg/mL, single-dose, prefilled glass syringe with attached 29-gauge, half-inch needle with a needle guard in cartons of 1 (NDC 0173-0892-42).
- 40 mg/0.4 mL, single-dose, prefilled glass syringe with attached 29-gauge, half-inch needle with a needle guard in cartons of 1 (NDC 0173-0904-42).

Prior to Dispensing: Refrigerate prefilled autoinjectors and prefilled syringes at 36°F to 46°F (2°C to 8°C). Keep the product in the original carton to protect from light. Do not freeze. Do not shake. Avoid exposure to heat.

Following Dispensing: Refrigerate prefilled autoinjectors and prefilled syringes at 36°F to 46°F (2°C to 8°C). Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Avoid exposure to heat.

If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days. Discard if left out of the refrigerator for more than 7 days.

NUCALA injection must be administered within 8 hours after removal from the carton. Discard if not administered within 8 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Instruct patients to contact their physicians if such reactions occur.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that NUCALA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Inform patients that herpes zoster infections have occurred in patients receiving NUCALA and where medically appropriate, inform patients that vaccination should be considered.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

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NCL:10PI

PHARMACIST—DETACH HERE AND GIVE PATIENT INFORMATION TO PATIENT

Patient Information

NUCALA (new KAH la)
(mepolizumab)
for injection, for subcutaneous use

NUCALA (new KAH la)
(mepolizumab)
injection, for subcutaneous use

What is NUCALA?

- NUCALA is a prescription medicine:
  - for the add-on maintenance treatment of severe asthma in people 6 years of age and older whose asthma is not controlled with their current asthma medicines. NUCALA helps prevent severe asthma attacks (exacerbations).
    NUCALA is not used to treat sudden breathing problems that occur with asthma.
  - for add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adults whose disease is not controlled with nasal corticosteroids. NUCALA helps reduce symptoms (e.g., nasal congestion, nasal discharge, mucus in the throat, loss of smell). NUCALA helps reduce the size of your nasal polyps and the use of oral corticosteroid medicines. NUCALA helps prevent surgery for your nasal polyps.
  - for the treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). NUCALA helps reduce symptoms and flares, and it may allow your healthcare provider to reduce your oral corticosteroid medicine.
  - for the treatment of people 12 years of age and older with hypereosinophilic syndrome (HES). NUCALA helps reduce symptoms and prevent flares.
- Medicines such as NUCALA reduce blood eosinophils. Eosinophils are a type of white blood cells that may contribute to your disease.

It is not known if NUCALA is safe and effective in children with severe asthma under 6 years of age.
It is not known if NUCALA is safe and effective in children and adolescents with CRSwNP or EGPA under 18 years of age.
It is not known if NUCALA is safe and effective in children with HES under 12 years of age.

Do not use NUCALA if you are allergic to mepolizumab or any of the ingredients in NUCALA. See the end of this leaflet for a complete list of ingredients in NUCALA.

Before receiving NUCALA, tell your healthcare provider about all of your medical conditions, including if you:

- have a parasitic (helminth) infection.
- are taking oral or inhaled corticosteroid medicines. **Do not** stop taking your corticosteroid medicines unless instructed by your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine to come back.
- are pregnant or plan to become pregnant. It is not known if NUCALA may harm your unborn baby.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will use NUCALA and breastfeed. You should not do both without talking with your healthcare provider first.
- Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
- Do not stop taking your other medicines unless instructed to do so by your healthcare provider.

How will I receive NUCALA?

Your healthcare provider will prescribe the dose that is right for you depending on what you are being treated for.

When injection is given by a healthcare provider:

- A healthcare provider will inject NUCALA under your skin (subcutaneously) every 4 weeks.

When injection is given by a patient or patient caregiver with a prefilled syringe or prefilled autoinjector:

- NUCALA may be prescribed as a single-dose prefilled autoinjector for people 12 years of age and older or as a single-dose prefilled syringe for people 6 years of age and older.
- Use NUCALA every 4 weeks exactly as your healthcare provider tells you to.
- Before you use NUCALA, your healthcare provider will show you or your caregiver how to give the injections.
- Read the Instructions for Use that comes with NUCALA for instructions about the right way to give your injections at home.
- You should inject NUCALA under your skin (subcutaneously) into your thigh or stomach (abdomen). Also, a caregiver may give the injection in the upper arm.
- If you miss a dose, inject a dose as soon as possible. Then continue (resume) your injection on your regular dosing schedule. If you do not notice that you have missed a dose until it is time for your next scheduled dose, then inject the next scheduled dose as planned. If you are not sure when to inject NUCALA, call your healthcare provider.

What are the possible side effects of NUCALA?

NUCALA can cause serious side effects, including:

- **allergic (hypersensitivity) reactions, including anaphylaxis.** Serious allergic reactions can happen after you get your NUCALA injection. Allergic reactions can sometimes happen hours or days after you get a dose of NUCALA. Tell your healthcare provider or get emergency help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, mouth, and tongue
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - hives
  - breathing problems
  - rash
- **herpes zoster infections.** Herpes zoster infections that can cause shingles have happened in people who received NUCALA.

The most common side effects of NUCALA include: headache, injection site reactions (pain, redness, swelling, itching, or a burning feeling at the injection site), back pain, and tiredness (fatigue). Mouth/throat pain and joint pain have been reported with CRSwNP.

These are not all of the possible side effects of NUCALA.

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

How should I store NUCALA?

- Store prefilled autoinjectors and prefilled syringes in the refrigerator between 36°F to 46°F (2°C to 8°C).

- Keep prefilled autoinjectors and prefilled syringes in the original carton until time of use to protect from light.
- Do not freeze. Do not shake. Keep away from heat.
- If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days.
- Safely throw away prefilled autoinjectors and prefilled syringes if the unopened carton is left out of the refrigerator for more than 7 days.
- Prefilled autoinjectors and prefilled syringes must be used within 8 hours after you take them out of the carton. Safely throw away if not used within 8 hours.
- Safely throw away medicine that is out of date or no longer needed.

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

General information about the safe and effective use of NUCALA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not give NUCALA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NUCALA that is written for health professionals.

What are the ingredients in NUCALA?

Active Ingredient: mepolizumab.

Inactive Ingredients (vials): polysorbate 80, sodium phosphate dibasic heptahydrate, and sucrose.

Inactive Ingredients (prefilled autoinjectors and prefilled syringes): citric acid monohydrate, EDTA disodium dihydrate, polysorbate 80, sodium phosphate dibasic heptahydrate, and sucrose.



For more information about NUCALA, call 1-888-825-5249 or visit our website at www.NUCALA.com.
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NCL:9PIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: March 2023

Instructions for Use

NUCALA
(mepolizumab)
injection, for subcutaneous use

100 mg/mL

Prefilled Autoinjector

Important information

NUCALA is a prescription medicine that is injected under the skin (subcutaneous) from a single-dose prefilled autoinjector. You and your caregiver should be trained on how to prepare and perform your injection before trying to do it yourself.

The following instructions provide the information you need to correctly use the prefilled autoinjector with yellow needle guard.

Before starting your injection, it is important that you read and understand these instructions and then carefully follow them so that you complete each step successfully.

Storage information

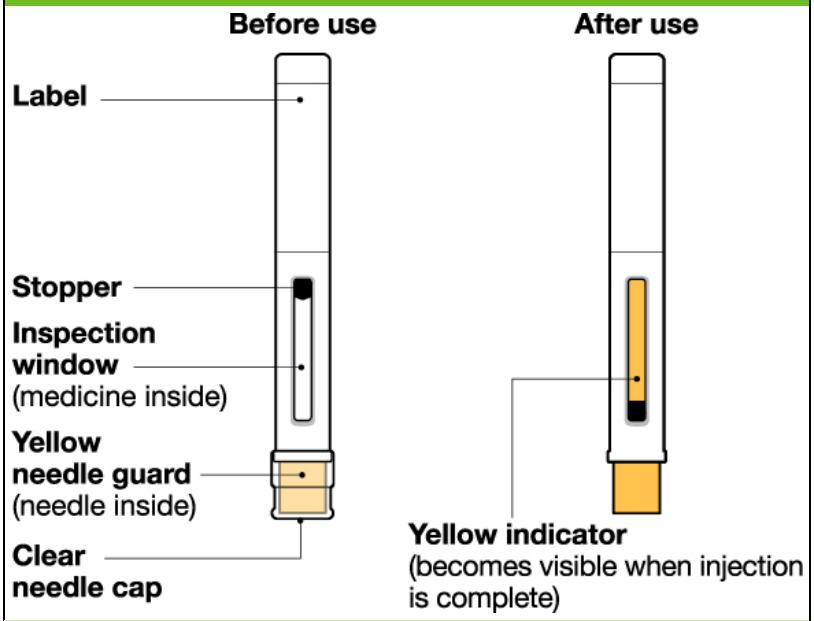
- Store in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep in the original carton until time of use to protect from light.
- **Do not** freeze. **Do not** shake. Keep away from heat.
- If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days.
- Safely throw away the prefilled autoinjector if it is left out of the refrigerator in the unopened carton for more than 7 days.
- The prefilled autoinjector must be used within 8 hours after you take it out of the carton. Safely throw it away if it is not used within 8 hours.
- Safely throw away medicine that is out of date or no longer needed.

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

Warnings

- **Do not** use the prefilled autoinjector more than 1 time. Throw away the autoinjector in an FDA-cleared sharps disposal container after your injection.
- **Do not** share the prefilled autoinjector with other people. You may give other people a serious infection, or you may get a serious infection from them.
- **Do not** use the prefilled autoinjector if it was dropped or looks damaged.

Know your prefilled autoinjector



Supplies in carton

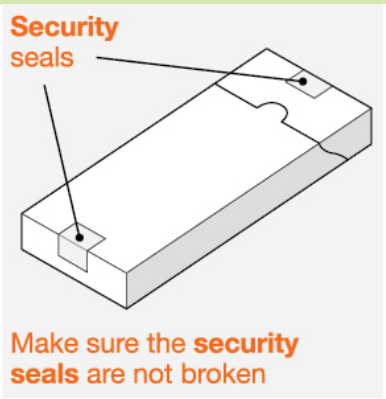
1 Prefilled autoinjector

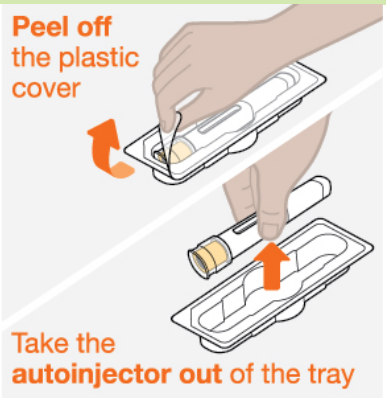
Supplies not in carton

- Alcohol swab
- Cotton ball or gauze
- Adhesive bandage
- Sharps disposal container
  (See Step 8 “Throw away your used autoinjector” at the end of this Instructions for Use for proper disposal instructions.)

Prepare

1. Take out the prefilled autoinjector

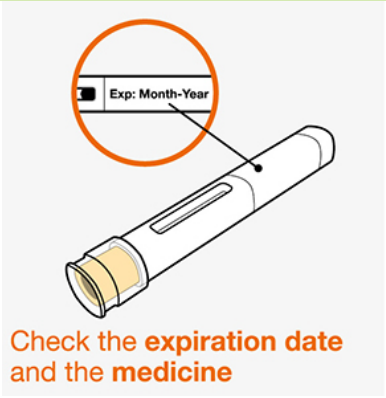




- Take the carton out of the refrigerator and make sure the security seals are not broken.
- Remove the tray from the carton.
- Peel off the clear plastic cover from the corner of the tray.

- Holding the middle of the prefilled autoinjector (near the inspection window), carefully take the prefilled autoinjector out of the tray.
- Place the prefilled autoinjector on a clean, flat surface at room temperature away from direct sunlight and out of the reach of children.
    - **Do not** use the prefilled autoinjector if the security seal on the carton is broken. Contact GSK for more information at 1-888-825-5249.
    - **Do not** remove the clear needle cap at this step.

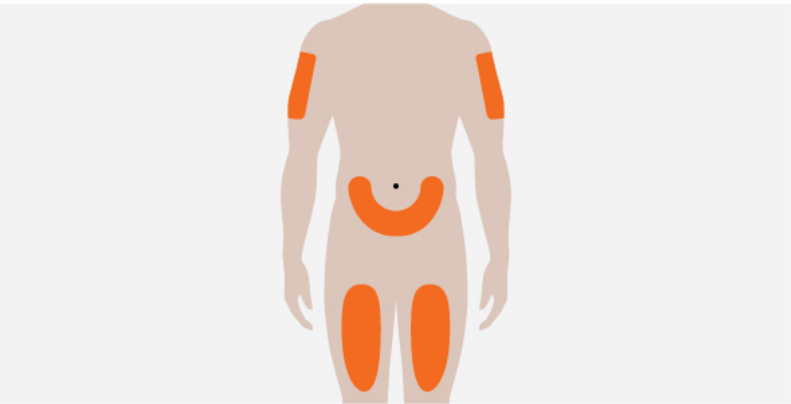
2. Inspect and wait 30 minutes before use





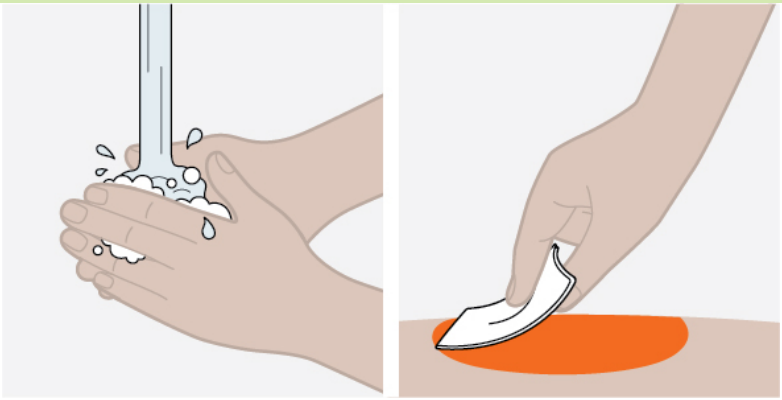
- Check that the expiration date on the label of the prefilled autoinjector has not passed.
- Look at the medicine in the inspection window. It should be clear to pale yellow to pale brown in color and without cloudiness or particles.
- It is normal to see 1 or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.
    - **Do not** use if the expiration date has passed.
    - **Do not** warm your prefilled autoinjector in a microwave, hot water, or direct sunlight.
    - **Do not** use if the medicine is cloudy or discolored, or has particles. Contact GSK for more information at 1-888-825-5249.
    - **Do not** use the prefilled autoinjector if it has been left out of the carton for more than 8 hours.

3. Choose your injection site



- You can inject in your thighs or abdomen.
- **If you are giving the injection to someone else as a caregiver or healthcare provider, you can also inject into their upper arm.**
- If you need more than 1 injection to complete your dose, leave at least 2 inches between each injection site.
    - **Do not** inject where your skin is bruised, tender, red, or hard.
    - **Do not** inject within 2 inches of your belly button.

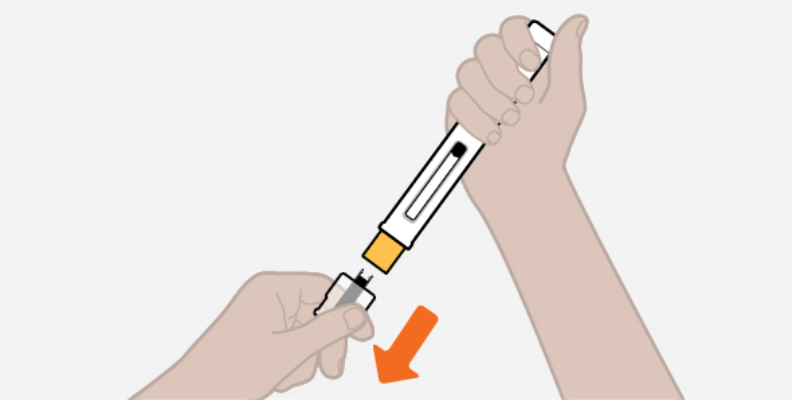
4. Clean your injection site



- Wash your hands with soap and water.
- Clean your injection site by wiping your skin with an alcohol swab and allowing your skin to air dry.
    - **Do not** touch your cleaned injection site again until you have finished your injection.

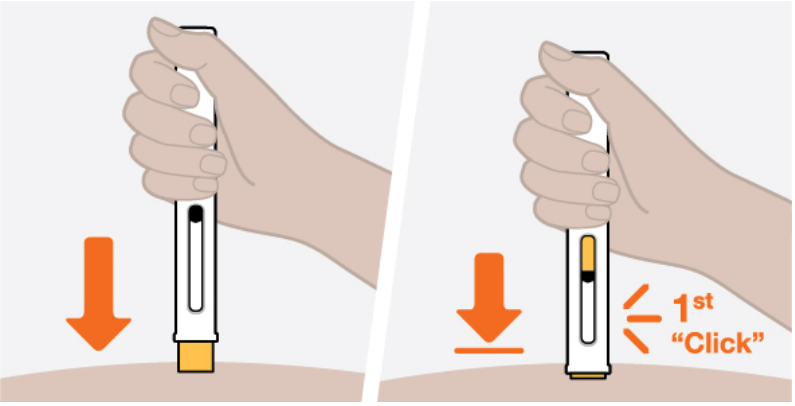
Inject

5. Remove the clear needle cap



- Remove the clear needle cap from the prefilled autoinjector by pulling it straight off, away from the yellow needle guard (as shown). It may take some force to remove the clear needle cap.
- You may see a drop of medicine at the end of the needle. This is normal.
- Make sure you inject within 5 minutes after you remove the clear needle cap.
    - **Do not** press the yellow needle guard with your fingers. This could activate the prefilled autoinjector too soon and cause a needle injury.
    - **Do not** put the clear needle cap back onto the prefilled autoinjector. This could accidentally start the injection.

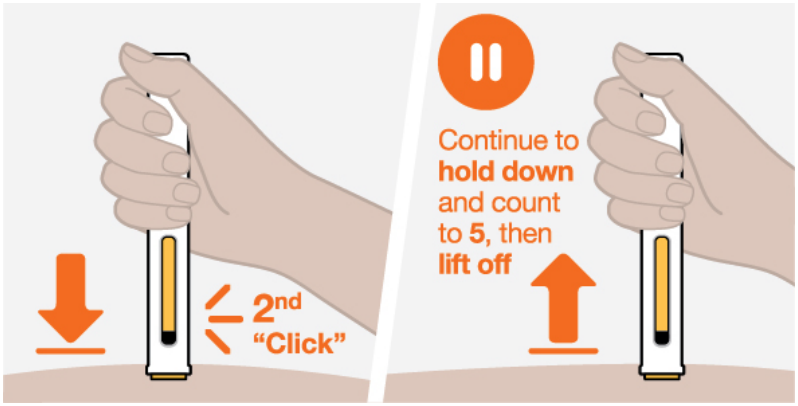
6. Start your injection



- Hold the prefilled autoinjector with its inspection window facing you.
- Place the prefilled autoinjector straight onto your injection site with the yellow needle guard flat on the surface of your skin, as shown.
- To start your injection, push the autoinjector all the way down and keep the autoinjector held down against your skin. This will make the yellow needle guard slide up into the autoinjector.
- You should hear the 1st click to let you know your injection has started.

- The yellow indicator will move down through the inspection window as you receive your dose.
    - **Do not** lift the autoinjector at this step as it may result in an incomplete injection.
    - **Do not** use the autoinjector if the yellow needle guard does not slide up into the autoinjector. Throw it away in an FDA-cleared sharps container.
    - **Do not** try to use the autoinjector upside down with the yellow needle guard facing upward against your thumb.

7. Complete your injection



- Your injection may take up to 15 seconds to complete.
- Continue to hold the autoinjector down until you hear the 2nd click, the stopper has stopped moving, and the inspection window is filled with the yellow indicator.
- After you hear the 2nd click, continue to hold and count to 5 before you lift the autoinjector away from your skin.
- If you do not hear the 2nd click:
    - check that the inspection window is filled with the yellow indicator, or
    - hold the autoinjector down for 15 seconds to make sure the injection is complete.
- There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive bandage if you need it.
    - **Do not** lift the autoinjector until you have heard the 2nd click, the window has been filled with the yellow indicator, and you have counted to 5.
    - **Do not** rub your injection site.
    - **Do not** put the clear needle cap back onto the autoinjector.

Dispose

8. Throw away your used autoinjector



Put your used autoinjector and clear needle cap in an FDA-cleared sharps disposal container right away after use.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic;
- able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
- upright and stable during use;
- leak-resistant; and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of it. There may be state or local laws about how you should throw away used autoinjectors.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at:

www.fda.gov/safesharpsdisposal.

- **Do not** throw away your used sharps disposal container in your household trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.

Keep your sharps disposal container out of the reach of children.

Frequently asked questions

1. **What happens if the medicine looks cloudy, the expiration date has passed, or the prefilled autoinjector looks damaged?**
   Contact GSK for more information at 1-888-825-5249.
2. **Can I change (rotate) the injection site for the prefilled autoinjector?**
   You may change (rotate) the site (thigh, abdomen, or upper arm) or move the autoinjector as long as you have not started pressing down. When the yellow needle guard is pressed, your injection will start right away.

3. **Why do I need to inject within 5 minutes of removing the clear needle cap?**
   This prevents the medicine from drying in the needle. It could affect how much medicine you get.
4. **What happens if I remove the autoinjector before the 2nd click, the stopper has stopped moving, or the inspection window is not filled with the yellow indicator?**
   If this happens, you may not have received your full dose. Contact GSK for more information at 1-888-825-5249.
5. **Who do I contact if I need help with my injection?**
   Your healthcare provider will be able to help you with any more questions you might have.

For more information about NUCALA, call 1-888-825-5249 or visit our website at www.NUCALA.com.

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NCL:4IFU-A

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: March 2023

Instructions for Use

NUCALA
(mepolizumab)
injection, for subcutaneous use

100 mg/mL

Prefilled Syringe

Important information

NUCALA is a prescription medicine that is injected under the skin (subcutaneous) from a single-dose prefilled syringe. You and your caregiver should be trained on how to prepare and perform your injection before trying to do it yourself.

The following instructions provide the information you need to correctly use the prefilled syringe with automatic needle guard.

Before starting your injection, it is important that you read and understand these instructions and then carefully follow them so that you complete each step successfully.

Storage information

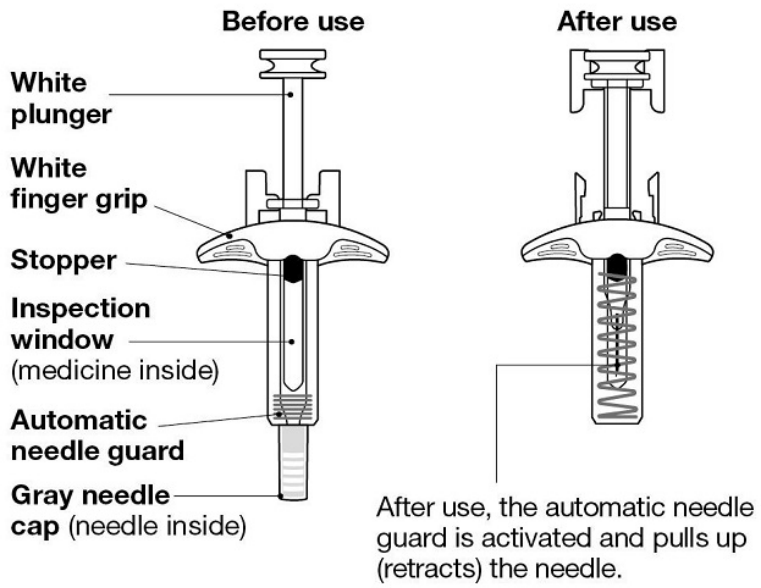
- Store in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep in the original carton until time of use to protect from light.
- **Do not** freeze. **Do not** shake. Keep away from heat.
- If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days.
- Safely throw away the prefilled syringe if it is left out of the refrigerator in the unopened carton for more than 7 days.
- The prefilled syringe must be used within 8 hours after you take it out of the carton. Safely throw it away if it is not used within 8 hours.
- Safely throw away medicine that is out of date or no longer needed.

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

Warnings

- **Do not** use the prefilled syringe more than 1 time. Throw away the syringe in an FDA-cleared sharps disposal container after your injection.
- **Do not** share the prefilled syringe with other people. You may give other people a serious infection, or you may get a serious infection from them.
- **Do not** use the prefilled syringe if it was dropped or looks damaged.

Know your prefilled syringe



Supplies in carton

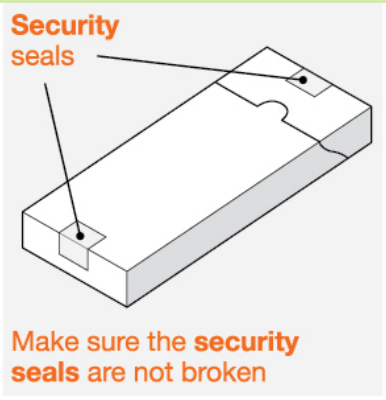
1 Prefilled syringe

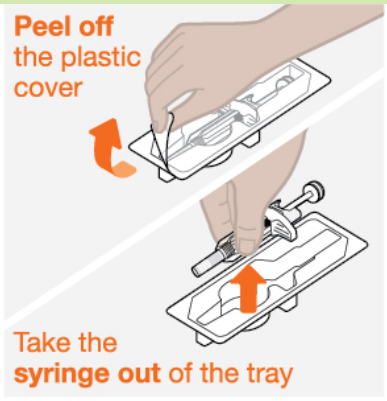
Supplies not in carton

- Alcohol swab
- Cotton ball or gauze
- Adhesive bandage
- Sharps disposal container
  (See Step 8 “Throw away your used syringe” at the end of this Instructions for Use for proper disposal instructions.)

Prepare

1. Take out the prefilled syringe





- Take the carton out of the refrigerator and make sure the security seals are not broken.
- Remove the tray from the carton.
- Peel off the clear plastic cover from the corner of the tray.

- Holding the middle of the prefilled syringe (near the inspection window), carefully take the prefilled syringe out of the tray.
- Place the prefilled syringe on a clean, flat surface at room temperature away from direct sunlight and out of the reach of children.
    - **Do not** use the prefilled syringe if the security seal on the carton is broken. Contact GSK for more information at 1-888-825-5249.
    - **Do not** remove the gray needle cap at this step.

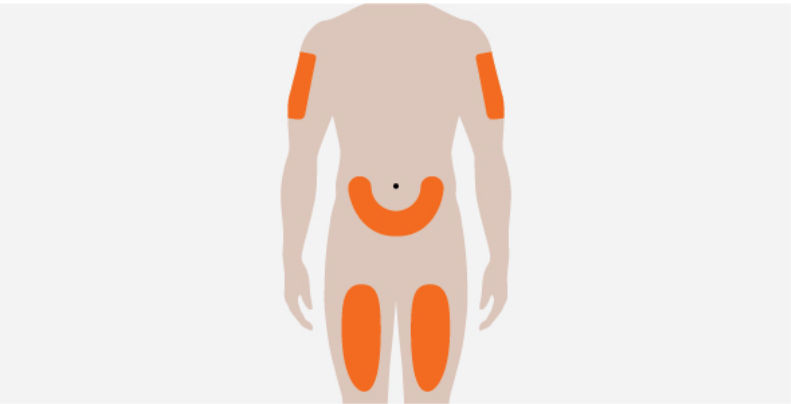
2. Inspect and wait 30 minutes before use





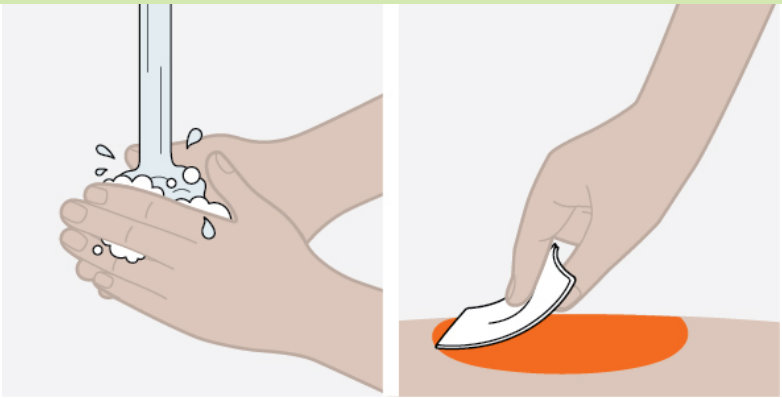
- Check that the expiration date on the label of the prefilled syringe has not passed.
- Look at the medicine in the inspection window. It should be clear to pale yellow to pale brown in color and without cloudiness or particles.
- It is normal to see 1 or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.
    - **Do not** use if the expiration date has passed.
    - **Do not** warm your prefilled syringe in a microwave, hot water, or direct sunlight.
    - **Do not** use if the medicine is cloudy or discolored, or has particles. Contact GSK for more information at 1-888-825-5249.
    - **Do not** use the prefilled syringe if it has been left out of the carton for more than 8 hours.

3. Choose your injection site



- You can inject in your thighs or abdomen.
- **If you are giving the injection to someone else as a caregiver or healthcare provider, you can also inject into their upper arm.**
- If you need more than 1 injection to complete your dose, leave at least 2 inches between each injection site.
    - **Do not** inject where your skin is bruised, tender, red, or hard.
    - **Do not** inject within 2 inches of your belly button.

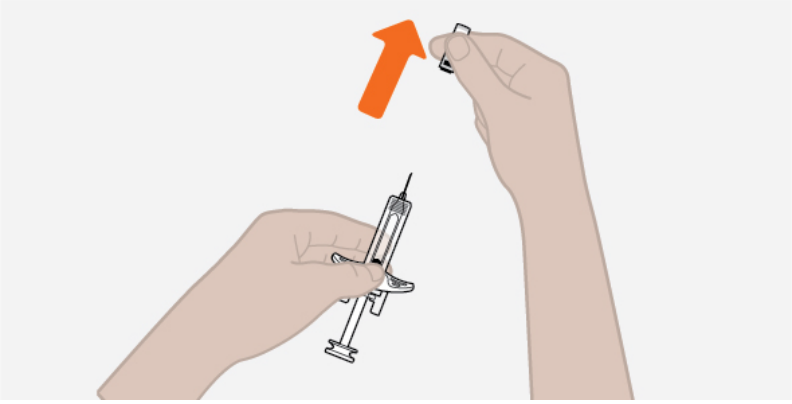
4. Clean your injection site



- Wash your hands with soap and water.
- Clean your injection site by wiping your skin with an alcohol swab and allowing your skin to air dry.
    - **Do not** touch your cleaned injection site again until you have finished your injection.

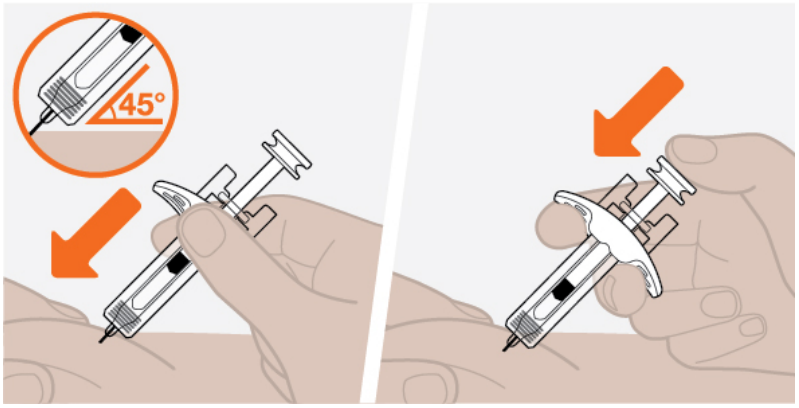
Inject

5. Remove the gray needle cap



- Remove the gray needle cap from the prefilled syringe by pulling it straight off, away from the needle (as shown). It may take some force to remove the gray needle cap.
- You may see a drop of medicine at the end of the needle. This is normal.
- Make sure you inject within 5 minutes after you remove the gray needle cap.
  - **Do not** let the needle touch any surface.
  - **Do not** touch the needle.
  - **Do not** touch the white plunger at this step. This could accidentally push medicine out, and you will not get your full dose.
  - **Do not** try to remove any air bubbles from the prefilled syringe.
  - **Do not** put the gray needle cap back onto the prefilled syringe. This could cause a needle injury.

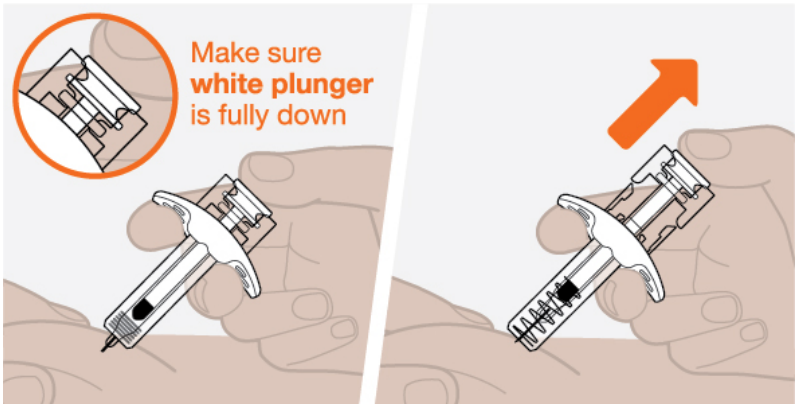
6. Start your injection



- Use your free hand to pinch the skin around your injection site. Keep pinching the skin throughout your injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.

- Move your thumb to the white plunger and use your other fingers to hold onto the white finger grip.
- Slowly push down on the white plunger to inject your full dose.

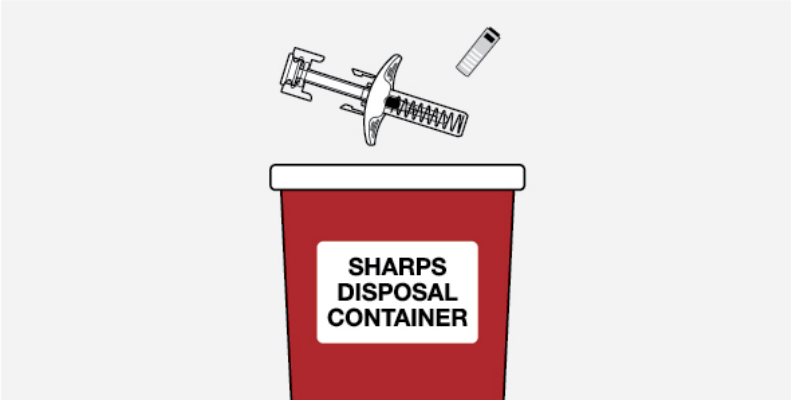
7. Complete your injection



- Make sure the white plunger is pushed all the way down until the stopper reaches the bottom of your syringe and all of the medicine is injected.
- Slowly lift your thumb up. This will allow the white plunger to come up and the needle to automatically retract (pull up) into the body of your syringe.
- After your injection is complete, release the pinched skin.
- There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive bandage if you need it.
    - **Do not** rub your injection site.
    - **Do not** put the gray needle cap back onto the syringe.

Dispose

8. Throw away your used syringe



Put your used syringe and gray needle cap in an FDA-cleared sharps disposal container right away after use.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic;

- able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
- upright and stable during use;
- leak-resistant; and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of it. There may be state or local laws about how you should throw away used syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at:

www.fda.gov/safesharpsdisposal.

- **Do not** throw away your used sharps disposal container in your household trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.

Keep your sharps disposal container out of the reach of children.

Frequently asked questions

1. **What happens if the medicine looks cloudy, the expiration date has passed, or the prefilled syringe looks damaged?**
   Contact GSK for more information at 1-888-825-5249.
2. **Can I change (rotate) the injection site for the prefilled syringe?**
   You may change (rotate) the site (thigh, abdomen, or upper arm) as long as you have not started injecting the medicine.
3. **Why do I need to inject within 5 minutes of removing the gray needle cap?**
   This prevents the medicine from drying in the needle. It could affect how much medicine you get.
4. **What happens if the needle does not retract (pull up) into the needle guard?**
   Right away and carefully put the syringe and needle cap in the FDA-cleared sharps disposal container and contact GSK for more information at 1-888-825-5249.
5. **Who do I contact if I need help with my injection?**
   Your healthcare provider will be able to help you with any more questions you might have.



For more information about NUCALA, call 1-888-825-5249 or visit our website at www.NUCALA.com.
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NCL:4IFU-S

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: March 2023

Instructions for Use

NUCALA
(mepolizumab)
injection, for subcutaneous use

40 mg/0.4 mL

Prefilled Syringe

Important information

NUCALA is a prescription medicine that is injected under the skin (subcutaneous) from a single-dose prefilled syringe. You should be trained on how to prepare and perform the injection before trying to do it yourself.

The following instructions provide the information you need to correctly use the prefilled syringe with automatic needle guard.

Before starting the injection, it is important that you read and understand these instructions and then carefully follow them so that you complete each step successfully.

Storage information

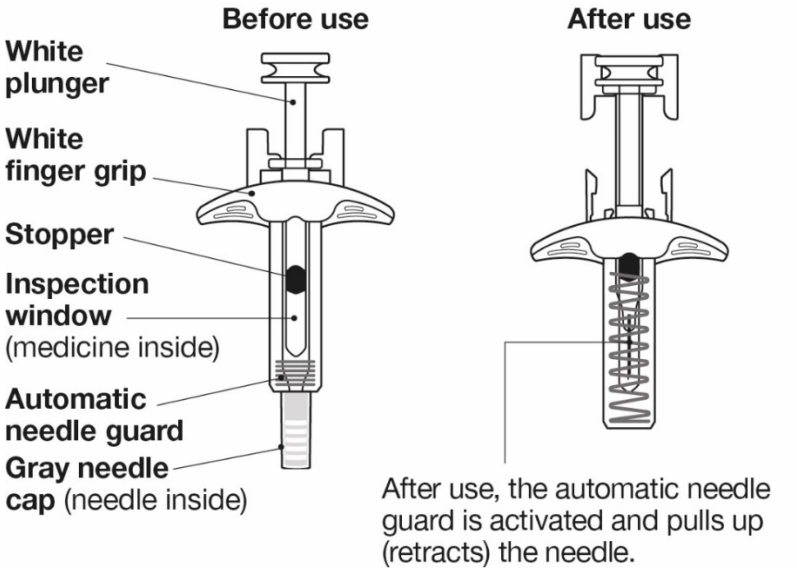
- Store in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep in the original carton until time of use to protect from light.
- **Do not** freeze. **Do not** shake. Keep away from heat.
- If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days.
- Safely throw away the prefilled syringe if it is left out of the refrigerator in the unopened carton for more than 7 days.
- The prefilled syringe must be used within 8 hours after you take it out of the carton. Safely throw it away if it is not used within 8 hours.
- Safely throw away medicine that is out of date or no longer needed.

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

Warnings

- **Do not** use the prefilled syringe more than 1 time. Throw away the syringe in an FDA-cleared sharps disposal container after the injection.
- **Do not** share the prefilled syringe with other people. You may give other people a serious infection, or you may get a serious infection from them.
- **Do not** use the prefilled syringe if it was dropped or looks damaged.

Know the prefilled syringe



Supplies in carton

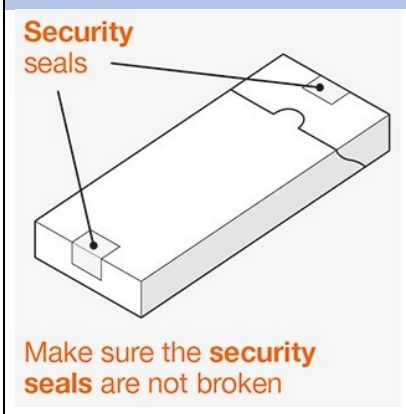
1 Prefilled syringe

Supplies not in carton

- Alcohol swab
- Cotton ball or gauze
- Adhesive bandage
- Sharps disposal container
  (See Step 8 “Throw away the used syringe” at the end of this Instructions for Use for proper disposal instructions.)

Prepare

1. Take out the prefilled syringe



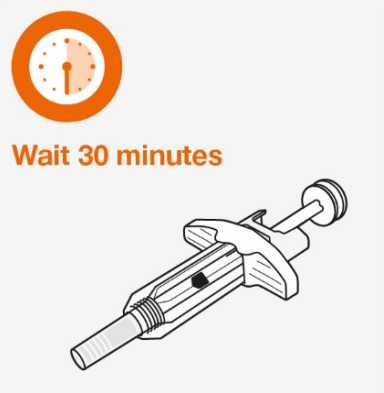


- Take the carton out of the refrigerator and make sure the security seals are not broken.
- Remove the tray from the carton.
- Peel off the clear plastic cover from the corner of the tray.
- Holding the middle of the prefilled syringe (near the inspection window), carefully take the prefilled syringe out of the tray.

- Place the prefilled syringe on a clean, flat surface at room temperature away from direct sunlight and out of the reach of children.
    - **Do not** use the prefilled syringe if the security seal on the carton is broken. Contact GSK for more information at 1-888-825-5249.
    - **Do not** remove the gray needle cap at this step.

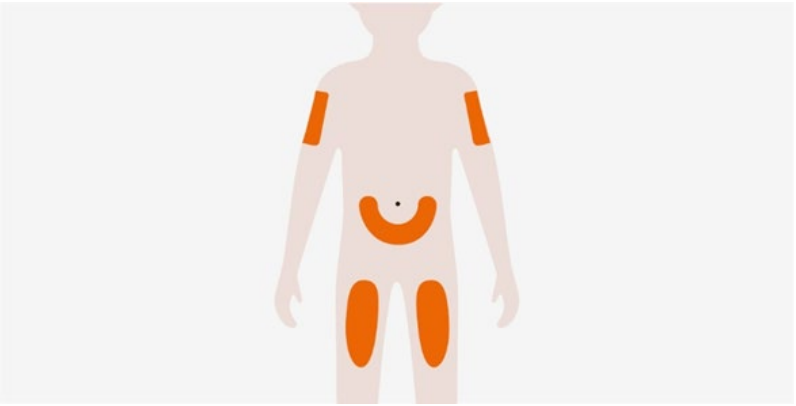
2. Inspect and wait 30 minutes before use





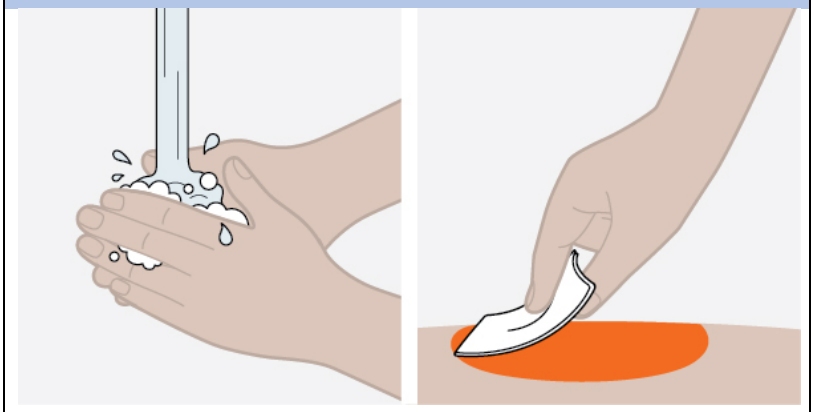
- Check that the expiration date on the label of the prefilled syringe has not passed.
- Look at the medicine in the inspection window. It should be clear to pale yellow to pale brown in color and without cloudiness or particles.
- It is normal to see 1 or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.
    - **Do not** use if the expiration date has passed.
    - **Do not** warm the prefilled syringe in a microwave, hot water, or direct sunlight.
    - **Do not** use if the medicine is cloudy or discolored, or has particles. Contact GSK for more information at 1-888-825-5249.
    - **Do not** use the prefilled syringe if it has been left out of the carton for more than 8 hours.

3. Choose the injection site



- You can inject in the thighs, abdomen, or upper arm.
    - **Do not** inject where the skin is bruised, tender, red, or hard.
    - **Do not** inject within 2 inches of the belly button.

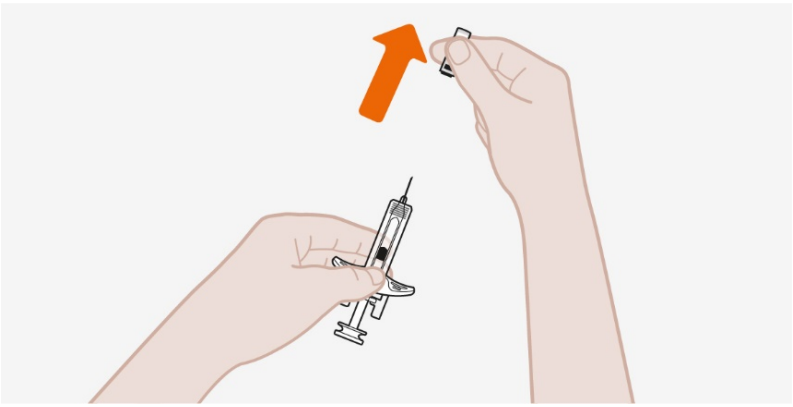
4. Clean the injection site



- Wash your hands with soap and water.
- Clean the injection site by wiping the skin with an alcohol swab and allowing the skin to air dry.
    - **Do not** touch the cleaned injection site again until you have finished the injection.

Inject

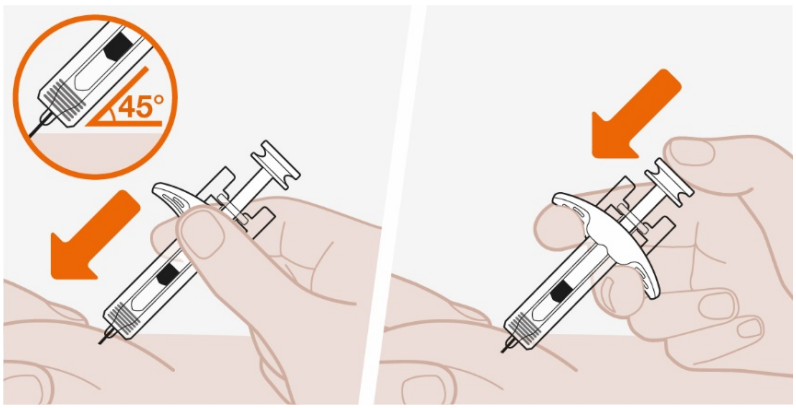
5. Remove the gray needle cap



- Remove the gray needle cap from the prefilled syringe by pulling it straight off, away from the needle (as shown). It may take some force to remove the gray needle cap.
- You may see a drop of medicine at the end of the needle. This is normal.
- Make sure you inject within 5 minutes after you remove the gray needle cap.
    - **Do not** let the needle touch any surface.
    - **Do not** touch the needle.
    - **Do not** touch the white plunger at this step. This could accidentally push medicine out, and the full dose will not be given.

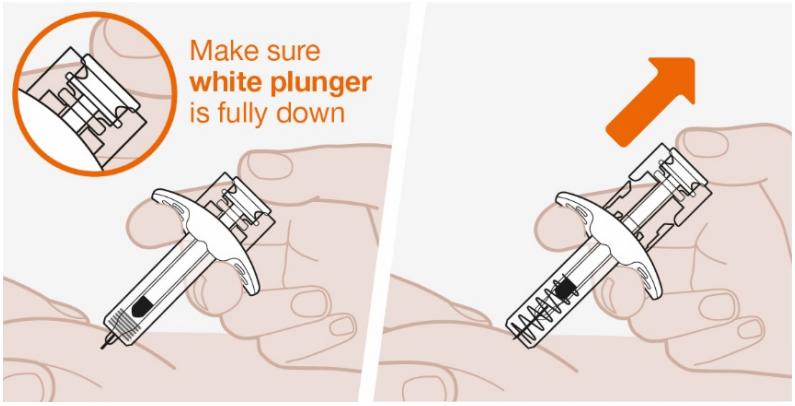
- **Do not** try to remove any air bubbles from the prefilled syringe.
- **Do not** put the gray needle cap back onto the prefilled syringe. This could cause a needle injury.

6. Start the injection



- Use your free hand to pinch the skin around the injection site. Keep pinching the skin throughout the injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the white plunger and use your other fingers to hold onto the white finger grip.
- Slowly push down on the white plunger to inject the full dose.

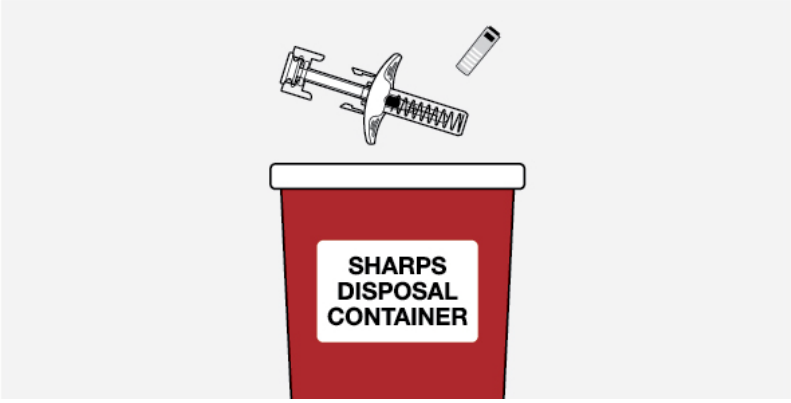
7. Complete the injection



- Make sure the white plunger is pushed all the way down until the stopper reaches the bottom of the syringe and all of the medicine is injected.
- Slowly lift your thumb up. This will allow the white plunger to come up and the needle to automatically retract (pull up) into the body of the syringe.
- After the injection is complete, release the pinched skin.
- There may be a small drop of blood at the injection site. This is normal. Press a cotton ball or gauze on the area and apply an adhesive bandage if you need it.
  - **Do not** rub the injection site.
  - **Do not** put the gray needle cap back onto the syringe.

Dispose

8. Throw away the used syringe



Put the used syringe and gray needle cap in an FDA-cleared sharps disposal container right away after use.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic;
- able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
- upright and stable during use;
- leak-resistant; and
- properly labeled to warn of hazardous waste inside the container.

When the sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of it. There may be state or local laws about how you should throw away used syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at:

www.fda.gov/safesharpsdisposal.

- **Do not** throw away the used sharps disposal container in your household trash unless your community guidelines permit this.
- **Do not** recycle the used sharps disposal container.

Keep the sharps disposal container out of the reach of children.

Frequently asked questions

1. **What happens if the medicine looks cloudy, the expiration date has passed, or the prefilled syringe looks damaged?**
   Contact GSK for more information at 1-888-825-5249.
2. **Can I change (rotate) the injection site for the prefilled syringe?**
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3. **Why do I need to inject within 5 minutes of removing the gray needle cap?**
   This prevents the medicine from drying in the needle. It could affect how much medicine you get.
4. **What happens if the needle does not retract (pull up) into the needle guard?**
   Right away and carefully put the syringe and needle cap in the FDA-cleared sharps disposal container and contact GSK for more information at 1-888-825-5249.
5. **Who do I contact if I need help with the injection?**
   The healthcare provider will be able to help you with any more questions you might have.

For more information about NUCALA, call 1-888-825-5249 or visit our website at www.NUCALA.com.

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NCL:2IFU-S40

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: March 2023

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
Nucala 100 mg solution for injection in pre-filled syringe
Nucala 40 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nucala 100 mg solution for injection in pre-filled pen

Each 1 ml pre-filled pen contains 100 mg of mepolizumab.

Nucala 100 mg solution for injection in pre-filled syringe

Each 1 ml pre-filled syringe contains 100 mg of mepolizumab.

Nucala 40 mg solution for injection in pre-filled syringe

Each 0.4 mL pre-filled syringe contains 40 mg of mepolizumab.

Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)
A clear to opalescent, colourless to pale yellow to pale brown solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe eosinophilic asthma

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see section 5.1).

4.2 Posology and method of administration

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, CRSwNP, EGPA or HES.

Posology

Severe eosinophilic asthma

Adults and adolescents aged 12 years and over

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old

The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.

CRSwNP

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

EGPA

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with EGPA was supported by modelling and simulation data (see section 5.2).

Children aged 6 to 11 years old weighing ⩾ 40 kg

The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old weighing < 40 kg

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and improvement of symptom control.
Patients who develop life-threatening manifestations of EGPA should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and level of symptom control.
Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

Special populations

Elderly patients

No dose adjustment is required for elderly patients (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Severe eosinophilic asthma

Children aged 6 to 11 years old

Nucala 100 mg powder for solution for injection and 40 mg solution for injection in pre-filled syringe are appropriate for administration to this population.

Nucala 100 mg solution for injection in pre-filled pen and 100 mg solution for injection in pre-filled syringe are not indicated for administration to this population.

Children less than 6 years old

The safety and efficacy of mepolizumab in children less than 6 years old have not yet been established.
No data are available.

CRSwNP in children less than 18 years old

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

EGPA in children less than 6 years old

The safety and efficacy of mepolizumab has not been established in children below the age of 6 years old.
No data are available.

HES in children aged less than 18 years old

The safety and efficacy of mepolizumab in children and adolescents aged less than 18 years old have not yet 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.

Method of administration

Nucala 100 mg solution for injection in pre-filled pen or pre-filled syringe

The pre-filled pen or pre-filled syringe should be used for subcutaneous injection only.

Nucala may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver are trained in injection techniques.

For children aged 6 to 11 years old, administration must be carried out by a healthcare professional or a trained caregiver.

For self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject Nucala into the upper arm.
For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled pen or pre-filled syringe are provided in the instructions for use in the package leaflet.

Nucala 40 mg solution for injection in pre-filled syringe

The pre-filled syringe should be used for subcutaneous injection only.

Nucala must be administered by a healthcare professional or a caregiver. It may be administered by a caregiver if a healthcare professional determines that it is appropriate, and the caregiver is trained in injection techniques.

The recommended injection sites are the upper arm, abdomen or thigh.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled syringe are provided in the instructions for use in the package leaflet.

4.3 Contraindications

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

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.

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

Asthma-related adverse symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of mepolizumab therapy is not recommended. Reduction in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

Hypersensitivity and administration-related reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment (see section 4.8). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Organ threatening or life-threatening EGPA

Nucala has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section 4.2).

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES (see section 4.2).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.
Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.

As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy.
Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

There are no data regarding the excretion of mepolizumab in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys at concentrations of less than 0.5% of those detected in plasma.

A decision must be made whether to discontinue breast-feeding or to discontinue Nucala therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Severe eosinophilic asthma

In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

CRSwNP

In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were headache (18%) and back pain (7%).

EGPA

In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES

In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n=263), from a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), in patients with EGPA receiving mepolizumab 300 mg SC (n=68), in a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years). The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

The frequency of adverse reactions is 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); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)*** Local injection site reactions Pyrexia	Common

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.
**From spontaneous post marketing reporting.

*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reactions

Systemic reactions, including hypersensitivity reactions, in CRSwNP

In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving mepolizumab 100 mg and in 1 patient (<1%) in the placebo group.

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic non-allergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In the placebo-controlled study, local injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.

EGPA
In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

Paediatric population

Severe eosinophilic asthma

Thirty-seven adolescents (aged 12-17) were enrolled in four placebo-controlled studies (25 mepolizumab treated intravenously or subcutaneously) of 24 to 52 weeks duration. Thirty -six paediatric patients (aged 6-11) received mepolizumab subcutaneously in an open-label study for 12 weeks. After a treatment interruption of 8 weeks, 30 of these patients, received mepolizumab for a further 52 weeks. The safety profile was similar to that seen in adults. No additional adverse reactions were identified.

HES

Four adolescents aged 12 to 17 years were enrolled in the placebo-controlled study 200622, one adolescent received 300 mg of mepolizumab, and 3 adolescents received placebo for 32 weeks. All 4 adolescents continued into a 20-week open-label extension study 205203 (see Section 5.1).

Reporting of suspected adverse reactions

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

4.9 Overdose

Single doses of up to 1 500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX09.

Mechanism of action

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

Severe eosinophilic asthma

In patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/µL at week 32 (n=182), a reduction of 84% compared to placebo. This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.
In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.
In adults, adolescents and children, this magnitude of reduction was observed within 4 weeks of treatment.

CRSwNP

In patients with CRSwNP, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 390 (n=206) to 60 cells/µL (n=126), which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period of 52 weeks.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/µL (n=64) at week 52. There was a geometric mean reduction of 83% compared to placebo and this magnitude of reduction was observed within 4 weeks of treatment.

HES

In patients with HES (adults/adolescents), following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1 460 (n=54) to 70 cells/µL (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, EGPA and HES

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents with severe refractory eosinophilic asthma treated with 100 mg dose, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults and adolescents with HES treated with 300 mg dose of mepolizumab subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.
The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) or in HES patients (n=102)

treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies.
In children aged 6 to 11 years old with severe refractory eosinophilic asthma following either 40 mg subcutaneously (for a weight < 40kg) or 100 mg subcutaneously (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study.
Neutralising antibodies were detected in one adult patient with severe refractory eosinophilic asthma and in no patients with CRSwNP, EGPA or HES. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Clinical efficacy

Severe eosinophilic asthma

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting beta$_2$ -adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1 192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV_1 was 60%. Patients continued to receive their existing asthma medicinal product during the studies.

For the oral corticosteroid-sparing study MEA115575, a total of 135 patients were enrolled (55% were female; mean age of 50 years) who were being treated daily with OCS (5-35 mg per day), and high-dose ICS plus an additional maintenance medicinal product.

Dose-ranging efficacy MEA112997 (DREAM) study

In MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 616 patients with severe refractory eosinophilic asthma, mepolizumab significantly reduced clinically significant asthma exacerbations (defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits) when administered in doses of 75 mg, 250 mg or 750 mg intravenously compared to placebo (see Table 1).

Table 1: Frequency of clinically significant exacerbations at week 52 in the intent to treat population

	Intravenous mepolizumab			Placebo
	75mg n=153	250mg n=152	750mg n=156	n= 155
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61(0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

Exacerbation reduction MEA115588 (MENSA) study

MEA115588 was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study which evaluated the efficacy and safety of mepolizumab as add-on therapy in 576 patients with severe refractory eosinophilic asthma defined as peripheral blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or greater than or equal to 300 cells/µL within the past 12 months.

Patients received mepolizumab 100 mg administered subcutaneously, mepolizumab 75 mg administered intravenously or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint was the frequency of clinically significant exacerbations of asthma and the reductions for both mepolizumab treatment arms compared to placebo were statistically significant (p<0.001). Table 2 provides the results of the primary and secondary endpoints for patients treated with subcutaneous mepolizumab or placebo.

Table 2: Results of primary and secondary endpoints at week 32 in the intent to treat population (MEA115588)

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Primary endpoint		
Frequency of clinically significant exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-
p-value	<0.001	
Secondary endpoints		
Frequency of exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Pre-bronchodilator FEV_1 (mL) at week 32		
Baseline (SD)	1 730 (659)	1 860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19. 5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

Table 3 shows the results of a combined analysis of the two exacerbation studies (MEA112997 and MEA115588) by baseline blood eosinophil count. The rate of exacerbations in the placebo arm increased with increasing baseline blood eosinophil count. The reduction rate with mepolizumab was greater in patients with higher blood eosinophil counts.

Table 3: Combined analysis of the rate of clinically significant exacerbations by baseline blood eosinophil count in patients with severe refractory eosinophilic asthma

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/μL		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
150 to <300 cells/μL		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.72 (0.47,1.10)	---
300 to <500 cells/μL		
n	109	76
Exacerbation rate per year	1.02	1.64
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
≥500 cells/μL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of ≥150/μL at baseline or a blood eosinophil count of ≥300/μL in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicinal product during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

A total of 135 patients were enrolled: mean age was 50 years, 55% were female, and 48% had been receiving oral steroid therapy for at least 5 years. The baseline mean prednisone equivalent dose was approximately 13 mg per day.

The primary endpoint was the percent reduction in daily OCS dose (weeks 20-24), whilst maintaining asthma control by defined dose reduction categories (see Table 4). Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the prednisone dose from the end of the optimisation phase. The comparison between mepolizumab and placebo was statistically significant (p=0.008).

Table 4: Results of the primary and secondary endpoints in MEA115575

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
Primary endpoint		
Percent reduction in OCS from baseline (weeks 20-24)		
90% - 100% 75% - <90% 50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	16 (23%) 12 (17%) 9 (13%) 7 (10%) 25 (36%)	7(11%) 5 (8%) 10 (15%) 7 (11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
Secondary endpoints (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0. 414	
Reduction in the daily OCS dose to ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Median % reduction in daily OCS dose from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Open-label extension studies in severe refractory eosinophilic asthma MEA115666 (COLUMBA), MEA115661 (COSMOS) and 201312 (COSMEX)

The long-term efficacy profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies MEA115666, MEA115661 and 201312 was generally consistent with the 3 placebo-controlled studies.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Study 205687 (SYNAPSE) was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP.
Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.

Key baseline characteristics included total endoscopic NP score mean (SD) 5.5 (1.29), nasal obstruction VAS score mean (SD) 9.0 (0.83), overall VAS symptom score mean (SD) 9.1 (0.74), loss of smell VAS score mean (SD) 9.7 (0.72) and Sino-Nasal Outcome Test (SNOT-22) mean (SD) 64.1 (18.32). The geometric mean eosinophil count was 390 cells/mcL (95% CI: 360, 420). In addition, 27% of patients had aspirin-exacerbated respiratory disease (AERD) and 48% of patients had at least 1 course of OCS for CRSwNP in the past 12 months.

Patients received a 100 mg dose of mepolizumab or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. The key secondary endpoint was the time to first NP surgery up to Week 52 (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [e.g. polypectomy] in the nasal cavity). Patients who received mepolizumab had significantly greater improvements (decreases) in total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo, and all secondary endpoints were statistically significant in favour of mepolizumab (see Table 5 and Figure 1).

Table 5: Summary of results for primary and secondary endpoints (intent to treat population)

	Placebo (N=201)	**Mepolizumab 100 mg SC (N=206)**
Co-primary endpoints		
Total endoscopic score at week 52 [a]		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52) [a]		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%)[d]	73 (36)	124 (60)
Key secondary endpoint		
Time to first nasal polyps surgery		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) [e]		0.43 (0.25, 0.76)
p-value [e]		0.003
Other secondary endpoints		
Overall VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%)[f]	40	64
SNOT-22 total score at week 52 [a, g]		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-16.49 (-23.57, -9.42)
≥28-point improvement (%)[f]	32	54

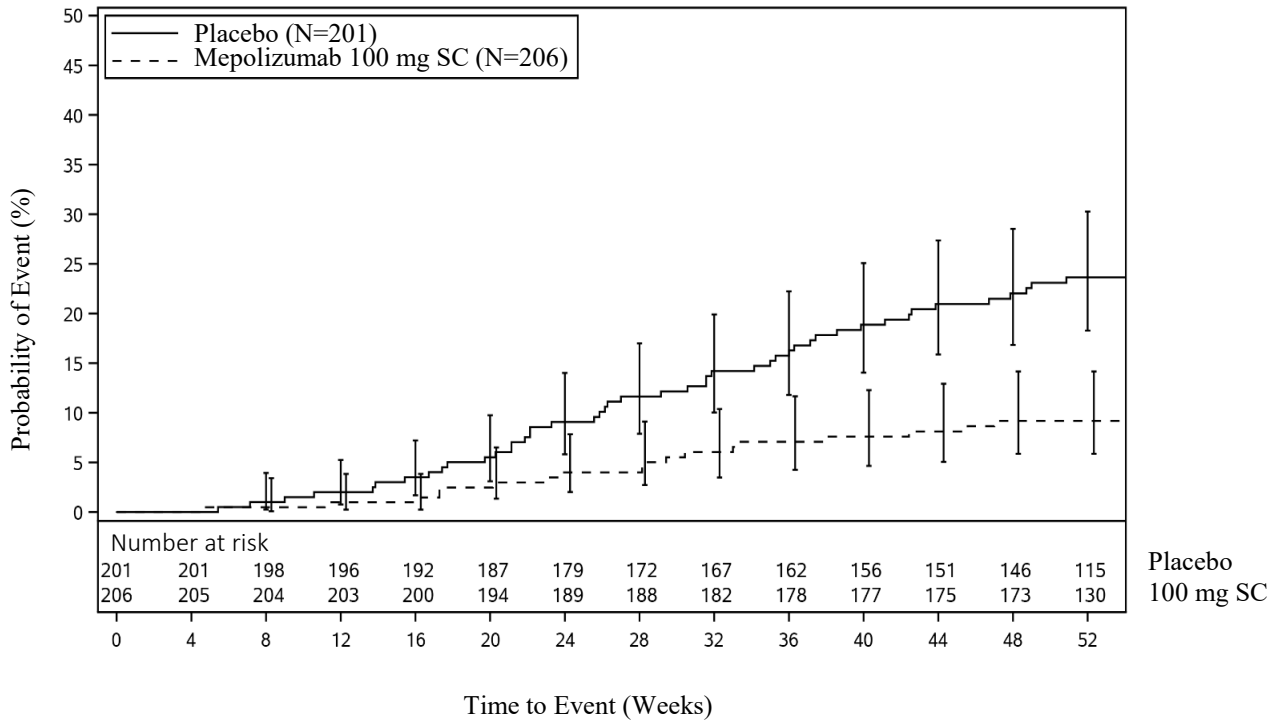
Patients requiring systemic corticosteroids for nasal polyps up to Week 52		
Number of patients with ≥1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI)[h]		0.58 (0.36, 0.92)
p-value[h]		0.020
Composite VAS score - nasal symptoms (Weeks 49-52) [a, i]		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
p-value [b]		<0.001
Difference in medians (95% CI)[c]		-2.68 (-3.44, -1.91)
≥2-point improvement (%)[f]	40	66
Loss of smell VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.37 (-0.65, -0.08)
≥3-point improvement (%) [f]	19	36

[a] Patients with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty were assigned their worst observed score prior to study withdrawal.
[b] Based on Wilcoxon rank-sum test.
[c] Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
[d] A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.
[e] Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).
[f] Threshold for improvement has been identified as a meaningful within-patient change for this assessment
[g] Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.
[h] Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.
[i] Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.

Time to first NP surgery

Across the 52-week treatment period, patients in the mepolizumab group had a lower probability of undergoing NP surgery than patients in the placebo group. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; p=0.003).

Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps Surgery



A post-hoc analysis of the proportion of patients with surgery showed a 61% reduction in the odds of surgery versus placebo (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

CRSwNP patients with co-morbid asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for mepolizumab 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic granulomatosis with polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life-threatening EGPA were excluded from study MEA115921.
Patients either received a 300 mg dose of mepolizumab or placebo administered subcutaneously once every 4 weeks in addition to their background prednisolone/prednisone with or without immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator.

Remission

The co- primary endpoints were the total accrued duration of remission, defined as a Birmingham Vasculitis Activity Score (BVAS) =0 plus prednisolone/prednisone dose ≤4 mg/day, and the

proportion of patients in remission at both 36 and 48 weeks of treatment. BVAS=0 represents no active vasculitis.

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 6).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

Using the secondary endpoint remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day, patients receiving mepolizumab 300 mg also achieved significantly greater accrued time in remission ($p<0.001$), and a higher proportion of patients were in remission at both Week 36 and Week 48 ($p<0.001$), compared to placebo.

Table 6: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	**Mepolizumab 300mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	3 (4)	9 (13)
24 to <36 weeks	0	10 (15)
≥36 weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
Patients in remission at Weeks 36 and 48	2 (3)	22 (32)
Odds ratio (mepolizumab/placebo)		16.74
95% CI	---	3.61, 77.56
p-value	---	<0.001

An odds ratio >1 favours mepolizumab. Remission: BVAS=0 and OCS dose ≤ 4mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg ($p<0.001$). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of ≤7.5 mg and ≤4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥12 years old with HES. Patients received 300 mg of mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.
Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥1 000 cells/μL during screening. Patients who were FIP1L1-PDGFRα kinase-positive were excluded from the study.
The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥2 occasions).
The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 7).
Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 2 and Table 8).

Table 7: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
Proportion of patients who experienced a HES flare		
Patients with ≥1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH =Cochran-Mantel-Haenszel

Time to first flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; p=0.002).

Figure 2: Kaplan Meier Curve for Time to First HES Flare

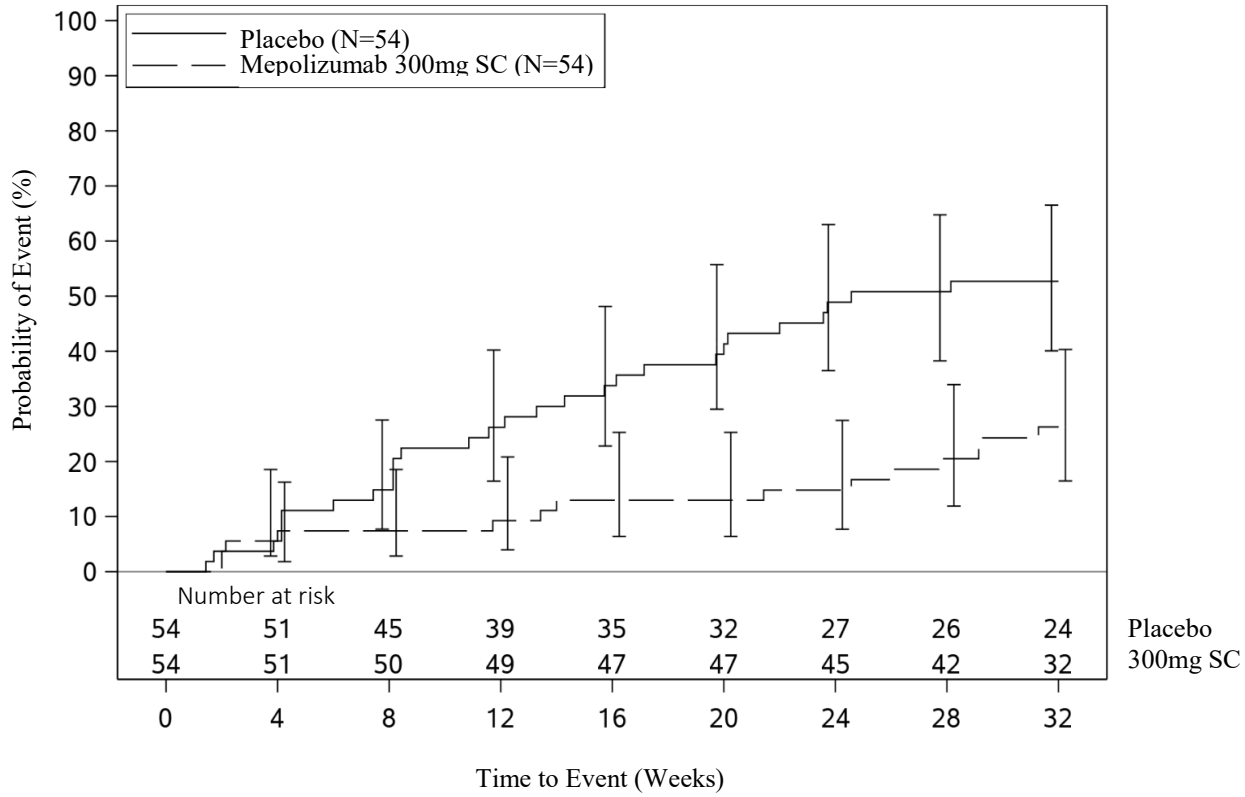


Table 8: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
HES flares during week 20 and up to and including week 32		
Patients with ≥1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI)[a]	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32[b]		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

[a] rate ratio <1 favours mepolizumab.
[b] patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine
CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.
In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of ≥50% during Weeks 16 to 20.

Paediatric population

Severe refractory eosinophilic asthma

In MEA115588 and in the double-blind placebo-controlled study 200862, there were 34 adolescents (12 to 17 years old). Of these 34 subjects: 12 received placebo, 9 received mepolizumab 75 mg intravenously, and 13 received 100 mg subcutaneously. In a combined analysis of these studies, a 40% reduction in clinically significant exacerbations was observed in adolescents following mepolizumab treatment compared to placebo (rate ratio 0.60; 95% CI: 0.17, 2.10).

Eosinophilic granulomatosis with polyangiitis (EGPA)

The are no clinical data available in children and adolescents aged 6 to 17 years old.

HES

Four adolescents (12 to 17 years old) were enrolled in study 200622; one adolescent received mepolizumab 300 mg, and 3 adolescents received placebo for 32 weeks. The one adolescent treated with mepolizumab in the 32-week Study 200622 did not have a HES flare. All 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 in which one of the 4 adolescents experienced one HES flare.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma and CRSwNP, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. Following administration of a single 100 mg subcutaneous dose in healthy subjects, mepolizumab systemic exposure was comparable between formulations.

Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration (T_{max}) ranging from 4 to 8 days.
Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single intravenous administration to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

Mepolizumab is a humanised IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special populations

Elderly patients (≥65 years old)

There are limited pharmacokinetic data available in elderly patients (≥65 years old) across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12 to 82 years.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Paediatric population

Severe eosinophilic asthma and HES

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma and 1 patient with HES). Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in patients aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in adolescent patients with severe refractory eosinophilic asthma or HES included in the phase 3 studies were consistent with adults (see section 4.2).

Paediatric pharmacokinetics following subcutaneous administration in patients 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg.
Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

EGPA

Mepolizumab pharmacokinetics in children (6 to 17 years old) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe eosinophilic asthma. The recommended posology in children 6 to 11 years old over a 15-70 kg broad weight range predicts that the exposure would remain on average within 26% of adults at 300 mg.

5.3 Preclinical safety data

As mepolizumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in monkeys. Intravenous and subcutaneous administration to monkeys was associated with reductions in peripheral and lung eosinophil counts, with no toxicological findings.

Eosinophils are thought to be associated with immune system responses to some parasitic infections. Studies conducted in mice treated with anti-IL-5 antibodies or genetically deficient in IL-5 or eosinophils have not shown impaired ability to clear parasitic infections. The relevance of these findings for humans is unknown.

Fertility

No impairment of fertility was observed in a fertility and general reproduction toxicity study in mice performed with an analogous antibody that inhibits IL-5 in mice. This study did not include a littering or functional offspring assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal and postnatal development (including immune function) of the offspring. Examinations for internal or skeletal malformations were not performed. Data in cynomolgus monkeys demonstrate that mepolizumab crossed the placenta. Concentrations of mepolizumab were about 1.2-2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Polysorbate 80
Disodium edetate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

If necessary, the pre-filled pen and pre-filled syringe(s) can be removed from the refrigerator and kept in the unopened pack for up to 7 days at room temperature (up to 30°C), when protected from light. The pack should be discarded if left out of the refrigerator for more than 7 days.

The pre-filled pen or pre-filled syringe(s) must be administered within 8 hours once the pack is opened. The pack should be discarded if not administered within 8 hours.

6.5 Nature and contents of container

Nucala 100 mg solution for injection in pre-filled pen

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Pack sizes:
1 pre-filled pen
Multipack containing 3 (3 packs of 1) pre-filled pens
Multipack containing 9 (9 packs of 1) pre-filled pens

Not all pack-sizes may be marketed.

Nucala 100 mg solution for injection in pre-filled syringe

1 ml solution in a Type 1 glass syringe with a fixed needle (stainless steel) and passive safety needle guard.

Pack sizes:
1 pre-filled syringe
Multipack containing 3 (3 packs of 1) pre-filled syringes
Multipack containing 9 (9 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

Nucala 40 mg solution for injection in pre-filled syringe

0.4 mL solution in a 1 mL Type 1 glass syringe with a fixed needle (stainless steel) and passive safety needle guard.

Pack sizes:
1 pre-filled syringe
Multipack containing 3 (3 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before administration, the solution should be inspected visually. The liquid should be clear to opalescent, colourless to pale yellow to pale brown. If the solution is cloudy, discoloured or contains particles, the solution should not be used.
After removing the pre-filled pen or pre-filled syringe(s) from the refrigerator, allow the pen or syringe(s) to reach room temperature for at least 30 minutes before injecting Nucala.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled pen or pre-filled syringe(s) are provided at the end of the package leaflet.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Nucala 100 mg solution for injection in pre-filled pen

EU/1/15/1043/003 1 pre-filled pen
EU/1/15/1043/004 3 (3 x 1) pre-filled pens (multipack)
EU/1/15/1043/007 9 (9 x 1) pre-filled pens (multipack)

Nucala 100 mg solution for injection in pre-filled syringe

EU/1/15/1043/005 1 pre-filled syringe
EU/1/15/1043/006 3 (3 x 1) pre-filled syringes (multipack)
EU/1/15/1043/008 9 (9 x 1) pre-filled syringes (multipack)

Nucala 40 mg solution for injection in pre-filled syringe

EU/1/15/1043/009 1 pre-filled syringe
EU/1/15/1043/010 3 (3 x 1) pre-filled syringes (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 December 2015
Date of latest renewal: 10 August 2020

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

Nucala 100 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg mepolizumab. After reconstitution, each ml of solution contains 100 mg mepolizumab.

Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

Lyophilised white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe eosinophilic asthma

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate control.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see section 5.1).

4.2 Posology and method of administration

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, CRSwNP, EGPA or HES.

Posology

Severe eosinophilic asthma

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old

The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.

CRSwNP

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

EGPA

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with EGPA was supported by modelling and simulation data (see section 5.2).

Children aged 6 to 11 years old weighing ⩾ 40 kg

The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old weighing < 40 kg

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and improvement of symptom control.
Patients who develop life-threatening manifestations of EGPA should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and level of symptom control.
Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

Special populations

Elderly patients

No dose adjustment is required for elderly patients (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Severe eosinophilic asthma

Children less than 6 years old

The safety and efficacy of mepolizumab in children less than 6 years old have not yet been established.
No data are available.

Children aged 6 to 17 years old

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with severe refractory eosinophilic asthma has been determined by limited efficacy, pharmacokinetic and pharmacodynamic studies and supported by modelling and simulation data (see sections 5.1 and 5.2).

CRSwNP in children less than 18 years old

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

EGPA in children less than 6 years old

The safety and efficacy of mepolizumab has not been established in children below the age of 6 years old.
No data are available.

HES in children aged less than 18 years old

The safety and efficacy of mepolizumab in children and adolescents aged less than 18 years old have not yet 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.

Method of administration

Nucala is for subcutaneous injection only and should be administered by a healthcare professional. It may be injected into the upper arm, thigh, or abdomen.

For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

The powder should be reconstituted prior to administration and the reconstituted solution should be used immediately. For instructions on the reconstitution of the medicinal product before administration, see section 6.6.
Each vial of mepolizumab should be used for a single patient, and any remainder of the vial should be discarded.

4.3 Contraindications

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

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.

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

Asthma-related adverse symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of mepolizumab therapy is not recommended. Reduction in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

Hypersensitivity and administration-related reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment (see section 4.8). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Organ threatening or life-threatening EGPA

Nucala has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section 4.2).

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES (see section 4.2).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.
Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.

As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy.
Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

There are no data regarding the excretion of mepolizumab in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys at concentrations of less than 0.5% of those detected in plasma.

A decision must be made whether to discontinue breast-feeding or to discontinue Nucala therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Severe eosinophilic asthma

In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

CRSwNP

In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were headache (18%) and back pain (7%).

EGPA

In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES

In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n= 263), from a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), in patients with EGPA receiving mepolizumab 300 mg SC (n=68), in a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years). The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

The frequency of adverse reactions is 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); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common

System Organ Class	Adverse reactions	Frequency
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)*** Local injection site reactions Pyrexia	Common

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies.. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.
**From spontaneous post marketing reporting.
*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reactions

Systemic reactions, including hypersensitivity reactions, in CRSwNP

In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving mepolizumab 100 mg and in 1 patient (<1%) in the placebo group.

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic non-allergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on

subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In the placebo-controlled study, local injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.

EGPA

In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

Paediatric population

Severe eosinophilic asthma

Thirty-seven adolescents (aged 12-17) were enrolled in four placebo-controlled studies (25 mepolizumab treated intravenously or subcutaneously) of 24 to 52 weeks duration. Thirty -six paediatric patients (aged 6-11) received mepolizumab subcutaneously in an open-label study for 12 weeks. After a treatment interruption of 8 weeks, 30 of these patients, received mepolizumab for a further 52 weeks. The safety profile was similar to that seen in adults. No additional adverse reactions were identified.

HES

Four adolescents aged 12 to 17 years were enrolled in the placebo-controlled study 200622, one adolescent received 300 mg of mepolizumab, and 3 adolescents received placebo for 32 weeks. All 4 adolescents continued into a 20-week open-label extension study 205203 (see Section 5.1).

Reporting of suspected adverse reactions

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

4.9 Overdose

Single doses of up to 1 500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX09.

Mechanism of action

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

Severe eosinophilic asthma

In patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/µL at week 32 (n=182), a reduction of 84% compared to placebo.
This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.
In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.
In adults, adolescents and children, this magnitude of reduction was observed within 4 weeks of treatment.

CRSwNP

In patients with CRSwNP, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 390 (n=206) to 60 cells/µL (n=126), which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period of 52 weeks.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/µL (n=64) at week 52. There was a geometric mean reduction of 83% compared to placebo and this magnitude of reduction was observed within 4 weeks of treatment.

HES

In patients with HES (adults/adolescents), following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks

of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1 460 (n=54) to 70 cells/µL (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, EGPA and HES

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents with severe refractory eosinophilic asthma treated with 100 mg dose, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults and adolescents with HES treated with 300 mg dose of mepolizumab subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.
The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) or in HES patients (n=102) treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies.
In children aged 6 to 11 years old with severe refractory eosinophilic asthma following either 40 mg subcutaneously (for a weight < 40kg) or 100 mg subcutaneously (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study. Neutralising antibodies were detected in one adult patient with severe refractory eosinophilic asthma and in no patients with CRSwNP, EGPA or HES. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Clinical efficacy

Severe eosinophilic asthma

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting $beta_2$-adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1 192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV_1 was 60%. Patients continued to receive their existing asthma medicinal product during the studies**.**

For the oral corticosteroid-sparing study MEA115575, a total of 135 patients were enrolled (55% were female; mean age of 50 years) who were being treated daily with OCS (5-35 mg per day), and high-dose ICS plus an additional maintenance medicinal product.

Dose-ranging efficacy MEA112997 (DREAM) study

In MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 616 patients with severe refractory eosinophilic asthma, mepolizumab significantly reduced clinically significant asthma exacerbations (defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits) when administered in doses of 75 mg, 250 mg or 750 mg intravenously compared to placebo (see Table 1).

Table 1: Frequency of clinically significant exacerbations at week 52 in the intent to treat population

	Intravenous mepolizumab			Placebo
	75mg n=153	250mg n=152	750mg n=156	n= 155
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61(0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

Exacerbation reduction MEA115588 (MENSA) study

MEA115588 was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study which evaluated the efficacy and safety of mepolizumab as add-on therapy in 576 patients with severe refractory eosinophilic asthma defined as peripheral blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or greater than or equal to 300 cells/µL within the past 12 months.

Patients received mepolizumab 100 mg administered subcutaneously, mepolizumab 75 mg administered intravenously or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint was the frequency of clinically significant exacerbations of asthma and the reductions for both mepolizumab treatment arms compared to placebo were statistically significant (p<0.001). Table 2 provides the results of the primary and secondary endpoints for patients treated with subcutaneous mepolizumab or placebo.

Table 2: Results of primary and secondary endpoints at week 32 in the intent to treat population (MEA115588)

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Primary endpoint		
Frequency of clinically significant exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-
p-value	<0.001	
Secondary endpoints		

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Frequency of exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	
Pre-bronchodilator FEV_1 (mL) at week 32		
Baseline (SD)	1 730 (659)	1 860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19. 5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

Table 3 shows the results of a combined analysis of the two exacerbation studies (MEA112997 and MEA115588) by baseline blood eosinophil count. The rate of exacerbations in the placebo arm increased with increasing baseline blood eosinophil count. The reduction rate with mepolizumab was greater in patients with higher blood eosinophil counts.

Table 3: Combined analysis of the rate of clinically significant exacerbations by baseline blood eosinophil count in patients with severe refractory eosinophilic asthma

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/μL		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
150 to <300 cells/μL		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
Rate ratio (95% CI)	0.72 (0.47,1.10)	---
300 to <500 cells/µL		
n	109	76
Exacerbation rate per year	1.02	1.64
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
≥500 cells/µL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of ≥150/µL at baseline or a blood eosinophil count of ≥300/µL in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicinal product during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

A total of 135 patients were enrolled: mean age was 50 years, 55% were female, and 48% had been receiving oral steroid therapy for at least 5 years. The baseline mean prednisone equivalent dose was approximately 13 mg per day.

The primary endpoint was the percent reduction in daily OCS dose (weeks 20-24), whilst maintaining asthma control by defined dose reduction categories (see Table 4). Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the prednisone dose from the end of the optimisation phase. The comparison between mepolizumab and placebo was statistically significant (p=0.008).

Table 4: Results of the primary and secondary endpoints in MEA115575

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
Primary endpoint		
Percent reduction in OCS from baseline (weeks 20-24)		
90% - 100% 75% - <90% 50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	16 (23%) 12 (17%) 9 (13%) 7 (10%) 25 (36%)	7 (11%) 5 (8%) 10 (15%) 7 (11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
p-value	0.008	
Secondary endpoints (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0. 414	
Reduction in the daily OCS dose to ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Median % reduction in daily OCS dose from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Open-label extension studies in severe refractory eosinophilic asthma MEA115666 (COLUMBA), MEA115661 (COSMOS) and 201312 (COSMEX)

The long-term efficacy profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies MEA115666, MEA115661 and 201312 was generally consistent with the 3 placebo-controlled studies.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Study 205687 (SYNAPSE) was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP.
Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.

Key baseline characteristics included total endoscopic NP score mean (SD) 5.5 (1.29), nasal obstruction VAS score mean (SD) 9.0 (0.83), overall VAS symptom score mean (SD) 9.1 (0.74), loss of smell VAS score mean (SD) 9.7 (0.72) and Sino-Nasal Outcome Test (SNOT-22) mean (SD) 64.1 (18.32). The geometric mean eosinophil count was 390 cells/mcL (95% CI: 360, 420). In addition, 27% of patients had aspirin-exacerbated respiratory disease (AERD) and 48% of patients had at least 1 course of OCS for CRSwNP in the past 12 months.

Patients received a 100 mg dose of mepolizumab or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. The key secondary endpoint was the time to first NP surgery up to Week 52 (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [e.g. polypectomy] in the nasal cavity). Patients who received mepolizumab had significantly greater improvements (decreases) in

total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo, and all secondary endpoints were statistically significant in favour of mepolizumab (see Table 5 and Figure 1).

Table 5: Summary of results for primary and secondary endpoints (intent to treat population)

	Placebo (N=201)	**Mepolizumab 100 mg SC (N=206)**
Co-primary endpoints		
Total endoscopic score at week 52 [a]		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52) [a]		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%)[d]	73 (36)	124 (60)
Key secondary endpoint		
Time to first nasal polyps surgery		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) [e]		0.43 (0.25, 0.76)
p-value [e]		0.003
Other secondary endpoints		
Overall VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%)[f]	40	64
SNOT-22 total score at week 52 [a, g]		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-16.49 (-23.57, -9.42)
≥28-point improvement (%)[f]	32	54

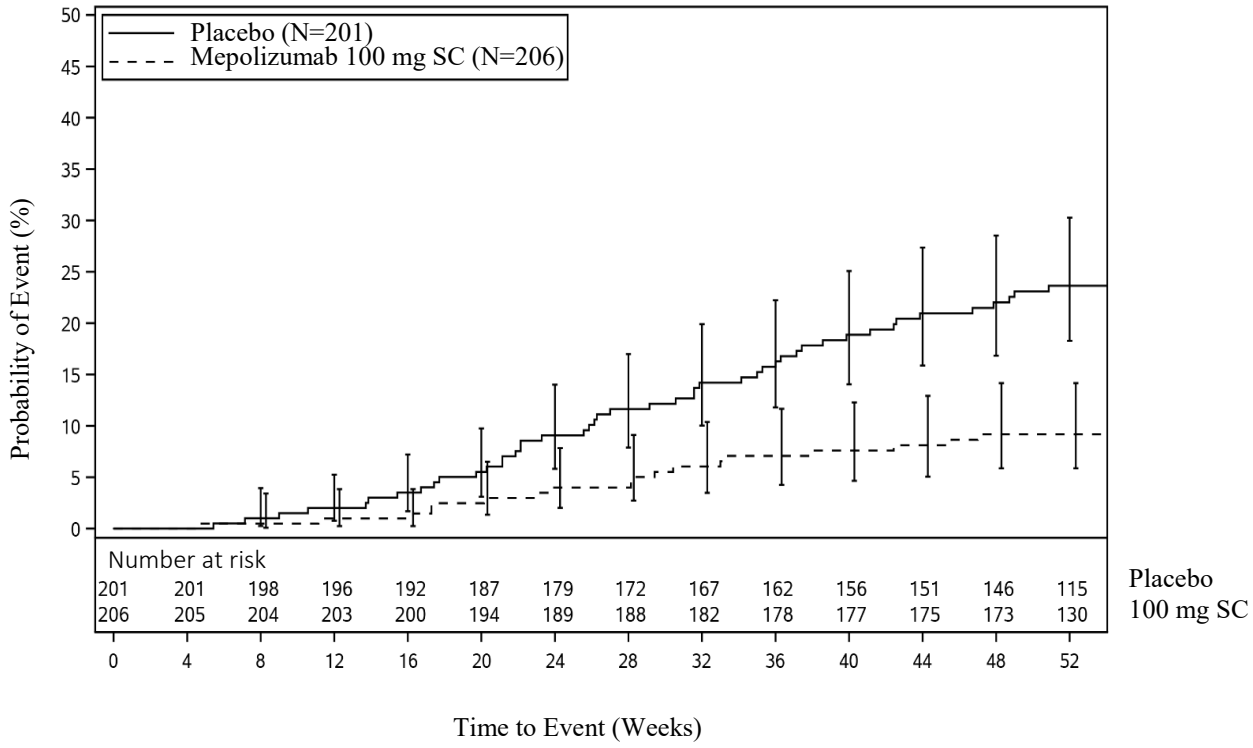
Patients requiring systemic corticosteroids for nasal polyps up to Week 52		
Number of patients with ≥1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI)[h]		0.58 (0.36, 0.92)
p-value[h]		0.020
Composite VAS score - nasal symptoms (Weeks 49-52) [a, i]		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
p-value [b]		<0.001
Difference in medians (95% CI)[c]		-2.68 (-3.44, -1.91)
≥2-point improvement (%)[f]	40	66
Loss of smell VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.37 (-0.65, -0.08)
≥3-point improvement (%) [f]	19	36

[a] Patients with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.
[b] Based on Wilcoxon rank-sum test.
[c] Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
[d] A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.
[e] Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).
[f] Threshold for improvement has been identified as a meaningful within-patient change for this assessment
[g] Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.
[h] Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.
[i] Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.

Time to first NP surgery

Across the 52-week treatment period, patients in the mepolizumab group had a lower probability of undergoing NP surgery than patients in the placebo group. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; p=0.003).

Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps Surgery



A post-hoc analysis of the proportion of patients with surgery showed a 61% reduction in the odds of surgery versus placebo (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

CRSwNP patients with co-morbid asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for mepolizumab 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic granulomatosis with polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life- threatening EGPA were excluded from study MEA115921.
Patients either received a 300 mg dose of mepolizumab or placebo administered subcutaneously once every 4 weeks in addition to their background prednisolone/prednisone with or without immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator.

Remission

The co- primary endpoints were the total accrued duration of remission, defined as a Birmingham Vasculitis Activity Score (BVAS) =0 plus prednisolone/prednisone dose ≤4 mg/day, and the proportion of patients in remission at both 36 and 48 weeks of treatment. BVAS=0 represents no active vasculitis.

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 6).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

Using the secondary endpoint remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day, patients receiving mepolizumab 300 mg also achieved significantly greater accrued time in remission (p<0.001), and a higher proportion of patients were in remission at both Week 36 and Week 48 (p<0.001), compared to placebo.

Table 6: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	**Mepolizumab 300mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	3 (4)	9 (13)
24 to <36 weeks	0	10 (15)
≥36 weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
Patients in remission at Weeks 36 and 48	2 (3)	22 (32)
Odds ratio (mepolizumab/placebo)		16.74
95% CI	---	3.61, 77.56
p-value	---	<0.001

An odds ratio >1 favours Nucala. Remission: BVAS=0 and OCS dose ≤ 4mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg (p<0.001). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of ≤ 7.5 mg and ≤ 4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥12 years old with HES. Patients received 300 mg of mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.
Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥1000 cells/μL during screening. Patients who were FIP1L1-PDGFRα kinase-positive were excluded from the study.
The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥ 2 occasions).
The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 7).
Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 2 and Table 8).

Table 7: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
Proportion of patients who experienced a HES flare		
Patients with ≥1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH =Cochran-Mantel-Haenszel

Time to first flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with Nucala compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; p=0.002).

Figure 2: Kaplan Meier Curve for Time to First HES Flare

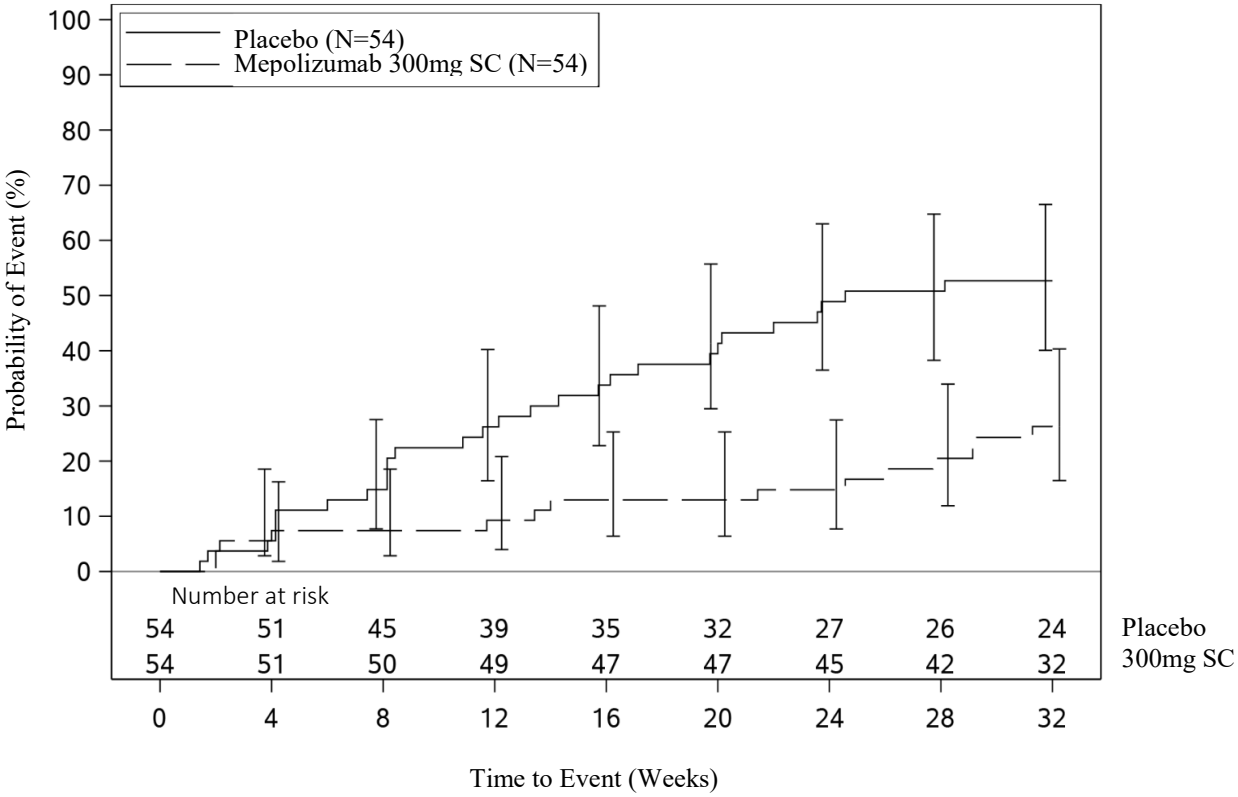


Table 8: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
HES flares during week 20 and up to and including week 32		
Patients with ≥1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI)[a]	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32[b]		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

[a] rate ratio <1 favours mepolizumab.
[b] patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine
CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.
In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of ≥50% during Weeks 16 to 20.

Paediatric population

Severe refractory eosinophilic asthma

In MEA115588 and in the double-blind placebo-controlled study 200862, there were 34 adolescents (12 to 17 years old). Of these 34 subjects: 12 received placebo, 9 received mepolizumab 75 mg intravenously, and 13 received 100 mg subcutaneously. In a combined analysis of these studies, a 40% reduction in clinically significant exacerbations was observed in adolescents following mepolizumab treatment compared to placebo (rate ratio 0.60; 95% CI: 0.17, 2.10).

Eosinophilic granulomatosis with polyangiitis (EGPA)

The are no clinical data available in children and adolescents aged 6 to 17 years old.

HES

Four adolescents (12 to 17 years old) were enrolled in study 200622; one adolescent received mepolizumab 300 mg, and 3 adolescents received placebo for 32 weeks. The one adolescent treated with mepolizumab in the 32-week Study 200622 did not have a HES flare. All 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 in which one of the 4 adolescents experienced one HES flare.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma and CRSwNP, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg.

Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration (T_{max}) ranging from 4 to 8 days.
Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single intravenous administration to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

Mepolizumab is a humanised IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special populations

Elderly patients (≥65 years old)

There are limited pharmacokinetic data available in elderly patients (≥65 years old) across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12 to 82 years.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Paediatric population

Severe eosinophilic asthma and HES

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma and 1 patient with HES). Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in patients aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in adolescent patients with severe refractory eosinophilic asthma or HES included in the phase 3 studies were consistent with adults (see section 4.2).

Paediatric pharmacokinetics following subcutaneous administration in patients 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following

subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg.
Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

EGPA

Mepolizumab pharmacokinetics in children (6 to 17 years old) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe eosinophilic asthma. The recommended posology in children 6 to 11 years old over a 15-70 kg broad weight range predicts that the exposure would remain on average within 26% of adults at 300 mg.

5.3 Preclinical safety data

As mepolizumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in monkeys. Intravenous and subcutaneous administration to monkeys was associated with reductions in peripheral and lung eosinophil counts, with no toxicological findings.

Eosinophils are thought to be associated with immune system responses to some parasitic infections. Studies conducted in mice treated with anti-IL-5 antibodies or genetically deficient in IL-5 or eosinophils have not shown impaired ability to clear parasitic infections. The relevance of these findings for humans is unknown.

Fertility

No impairment of fertility was observed in a fertility and general reproduction toxicity study in mice performed with an analogous antibody that inhibits IL-5 in mice. This study did not include a littering or functional offspring assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal and postnatal development (including immune function) of the offspring. Examinations for internal or skeletal malformations were not performed. Data in cynomolgus monkeys demonstrate that mepolizumab crossed the placenta. Concentrations of mepolizumab were about 1.2-2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Polysorbate 80

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

After reconstitution

Chemical and physical stability of the reconstituted medicinal product have been demonstrated for 8 hours when stored below 30°C.

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

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
Keep the vial in the outer carton 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

Clear, colourless 10 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with a plastic flip-cap containing 100 mg powder for solution for injection.

Pack sizes:
1 vial
Multipack containing 3 (3 packs of 1) vials

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution should be carried out under aseptic conditions.

Instructions for reconstitution for each vial

1. **Reconstitute the contents of the vial with 1.2 mL of sterile water for injections** preferably using a 2 to 3 mL syringe and a 21 gauge needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

   *Note: The reconstituted solution **must not be shaken** during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the sterile water has been added, but it may take additional time.*

2. If a mechanical reconstitution device (swirler) is used to reconstitute Nucala, reconstitution can

be accomplished by swirling at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1 000 rpm for no longer than 5 minutes is acceptable.

3. Following reconstitution, Nucala should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be used.
4. The reconstituted solution, if not used immediately must be:
    - Protected from sunlight
    - Stored below 30°C, not frozen
    - Discarded if not used within 8 hours of reconstitution

Instructions for administration of 100 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 1 mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

If more than one vial is required for administration of the prescribed dosage, repeat steps 1 to 3. It is recommended that individual injection sites are separated by at least 5 cm.

Instructions for administration of 40 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 0.4mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation. Dispose of the remaining solution.
3. Administer the 0.4mL injection (equivalent to 40 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/001
EU/1/15/1043/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 December 2015
Date of latest renewal: 10 August 2020

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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

Name and address of the manufacturers of the biological active substance

GlaxoSmithKline LLC
893 River Road
Conshohocken,
PA 19428
United States

Or

Human Genome Sciences, Inc.
9911 Belward Campus Drive
Rockville, MD 20850
United States

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana No. 90,
Torrile, 43056, Parma,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

1 pre-filled pen.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store pen in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

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 FOR PRE-FILLED PEN MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen
Multipack: 3 (3 packs of 1) pre-filled pens
Multipack: 9 (9 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store pen in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/004 (3 x 1 pre-filled pens)
EU/1/15/1043/007 (9 x 1 pre-filled pens)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON - PRE-FILLED PEN MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

1 pre-filled pen. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store pen in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Nucala 100 mg injection
mepolizumab
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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 100 mg syringe

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– FOR PRE-FILLED SYRINGE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 3 (3 packs of 1) pre-filled syringes
Multipack: 9 (9 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/006 (3 x 1 pre-filled syringes)
EU/1/15/1043/008 (9 x 1 pre-filled syringes)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 100 mg syringe

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON – PRE-FILLED SYRINGE MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 100 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Nucala 100 mg injection
mepolizumab
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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 40 mg syringe

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– FOR PRE-FILLED SYRINGE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 3 (3 packs of 1) pre-filled syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 40 mg syringe

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON – PRE-FILLED SYRINGE MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store syringe in the original carton in order to protect from light.
Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 40 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Nucala 40 mg injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (INDIVIDUAL PACKS INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.
Store in the original container 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

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12 Riverwalk
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Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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 OUTER PACKAGING

MULTIPACK CARTON (3 PACKS OF 1 VIAL – WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
Multipack: 3 (3 packs of 1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Do not freeze.
Store in the original container 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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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

CARTON (MULTIPACK ONLY WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection 1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

PRESS HERE TO OPEN

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Do not freeze.
Store in the original container 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

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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

Nucala 100 mg powder for solution for injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nucala 100 mg solution for injection in pre-filled pen

mepolizumab

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.
- 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 Nucala is and what it is used for
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

Mepolizumab, the active substance in Nucala, blocks a protein called *interleukin-5*. By blocking the action of this protein, it limits the production of eosinophils from the bone marrow and lowers the number of eosinophils in the bloodstream and the lungs.

Severe eosinophilic asthma

Some people with severe asthma have too many *eosinophils* (a type of white blood cell) in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma Nucala can treat.

Nucala can reduce your number of asthma attacks, if you or your child are already using medicines such as high dose inhalers, but your asthma is not well controlled by these medicines.
If you are taking medicines called *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your asthma.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood, and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps.
Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin**.**
Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

2. What you need to know before you use Nucala

Do not use Nucala:
- if you are **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

➔ **Tell your doctor or nurse** if your asthma remains uncontrolled, or gets worse, after you start Nucala treatment.

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body (see section 4, 'Possible side effects').

If you may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you are given Nucala.

Parasitic infections
Nucala may weaken your resistance to infections caused by parasites. If you already have a parasitic infection; it should be treated before you start treatment with Nucala. If you live in a region where these infections are common or if you are travelling to such a region:

➔ **Check with your doctor** if you think any of these may apply to you.

Children and adolescents

Severe eosinophilic asthma

The pre-filled pen is not intended for use in **children below 12 years of age** for the treatment of severe eosinophilic asthma.
For children aged 6-11 years, contact your doctor who will prescribe the recommended dose of Nucala which will be administered by a nurse or doctor.

CRSwNP

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

EGPA

This medicine is not intended for use in **children below 6 years of age** for the treatment of EGPA.

HES

This medicine is not intended for use in **adolescents or children below 18 years of age** for the treatment of HES.

Other medicines and Nucala
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma, CRSwNP, EGPA or HES

- **Don't suddenly stop taking** your existing medicines for your asthma, CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Nucala.

Pregnancy and breast-feeding
If you are pregnant, if you think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use Nucala.

Driving and using machines
The possible side effects of Nucala are unlikely to affect your ability to drive or use machines.

Nucala contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you or your caregiver can inject Nucala. If appropriate, they will then provide training to show you or your caregiver the correct way to use Nucala.

Nucala must be given to children aged 6 to 11 years by a doctor, nurse or trained caregiver.

Severe eosinophilic asthma

The recommended dose for adults and adolescents aged 12 years and older is 100 mg. You will have 1 injection every four weeks.

CRSwNP

The recommended dose for adults is 100 mg. You will have 1 injection every four weeks.

EGPA

The recommended dose for adults and adolescents aged 12 years and older is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:
The recommended dose is 200 mg. You will have 2 injections every four weeks.

Children weighing less than 40 kg:
The recommended dose is 100 mg. You will have 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

The recommended dose for adults is 300 mg. You will have 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

Instructions for using the pre-filled pen are given on the other side of this leaflet.

If you use more Nucala than you should
If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed
You or your caregiver should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time for your next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala
Do not stop injections of Nucala unless your doctor advises you to. Interrupting or stopping the treatment with Nucala may cause your symptoms and attacks to come back.

If your symptoms get worse while receiving injections of Nucala
➔ **Call your doctor**.

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. The side effects caused by Nucala are usually mild to moderate but can occasionally be serious.

Allergic reactions
Some people may have allergic or allergic-like reactions. These reactions may be common (they can affect **up to 1 in 10 people).** They usually occur within minutes to hours after the injection, but sometimes symptoms can start up to several days later.

Symptoms can include:
- chest tightness, cough, difficulty breathing
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- swelling of eyelids, face, lips, tongue or mouth
- hives
- rash

➔ **Seek medical attention immediately** if you think you (or your child) may be having a reaction.

If you may have had a similar reaction to any injection or medicine:
➔ **Tell your doctor** before you (or your child) are given Nucala.

Other side effects include:

Very common:
may affect more than 1 in 10 people
- headache

Common:
may affect up to 1 in 10 people
- chest infection - symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare:
may affect up to 1 in 1 000 people
- severe allergic reactions (*anaphylaxis*)

➔ **Tell your doctor or a nurse immediately** if you get any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor 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 Nucala

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

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

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

The Nucala pre-filled pen can be removed from the refrigerator and kept in its unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

6. Contents of the pack and other information

What Nucala contains
The active substance is mepolizumab.

Each 1 mL pre-filled pen contains 100 mg of mepolizumab.
The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 1 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled pen.

Nucala is available in a pack containing 1 pre-filled pen, or in a multipack comprised of 3 x 1 pre-filled pens or 9 x 1 pre-filled pens.

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12 Riverwalk
Citywest Business Campus
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Manufacturer
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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 web site: http://www.ema.europa.eu.

7. Step by step instructions for using the pre-filled pen

Administer once every four weeks.

Follow these instructions on how to use the pre-filled pen. Failure to follow these instructions may affect proper function of the pre-filled pen. You should also receive training on how to use the pre-filled pen. Nucala pre-filled pen is for use **under the skin only** (subcutaneous).

How to store Nucala

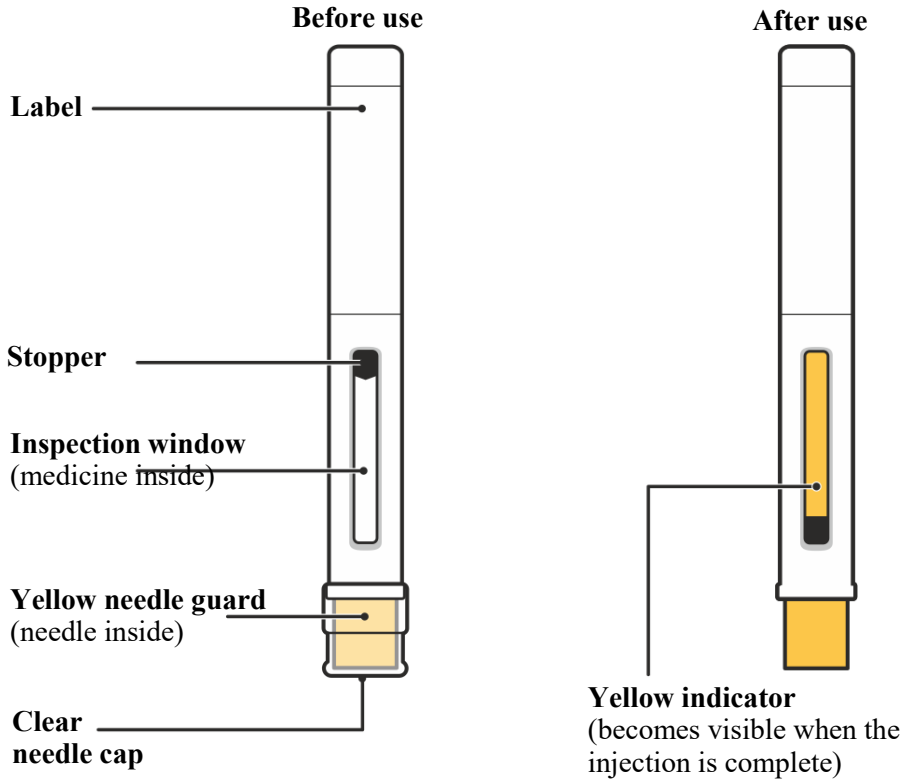
- Keep refrigerated before use.
- Do not freeze
- Keep the pre-filled pen in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled pen may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pen away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use Nucala

The pre-filled pen should be used only once and then discarded.

- **Do not** share your Nucala pre-filled pen with another person.
- **Do not** shake the pen.
- **Do not** use the pen if dropped onto a hard surface.
- **Do not** use the pen if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled pen



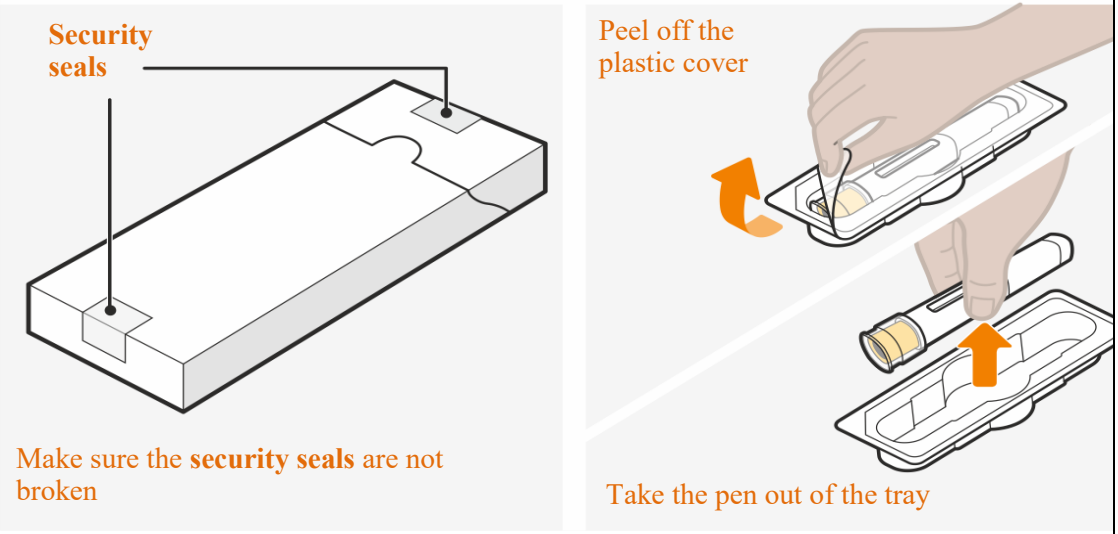
Prepare

1.Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled pen
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

2. Take out your pre-filled pen

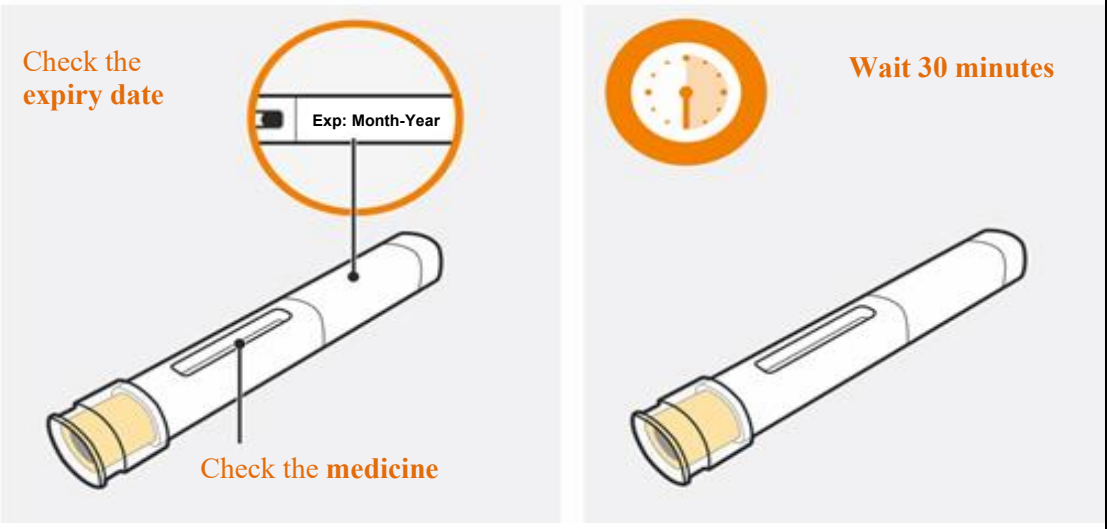


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the pen, carefully take it out of the tray.
- Place the pen on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the pen if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use

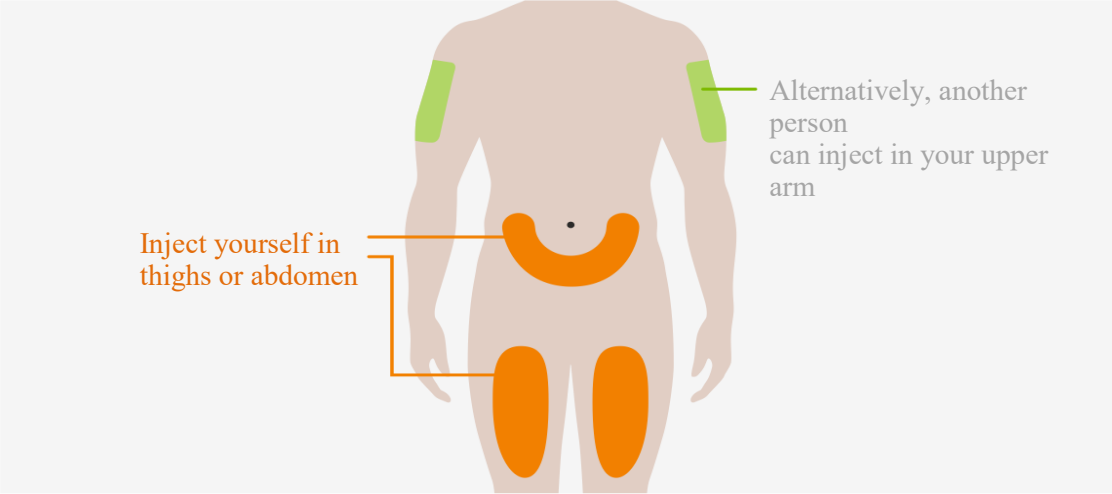


- Check the expiry date on the label of the pen.

- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the pen in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the pen if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step.

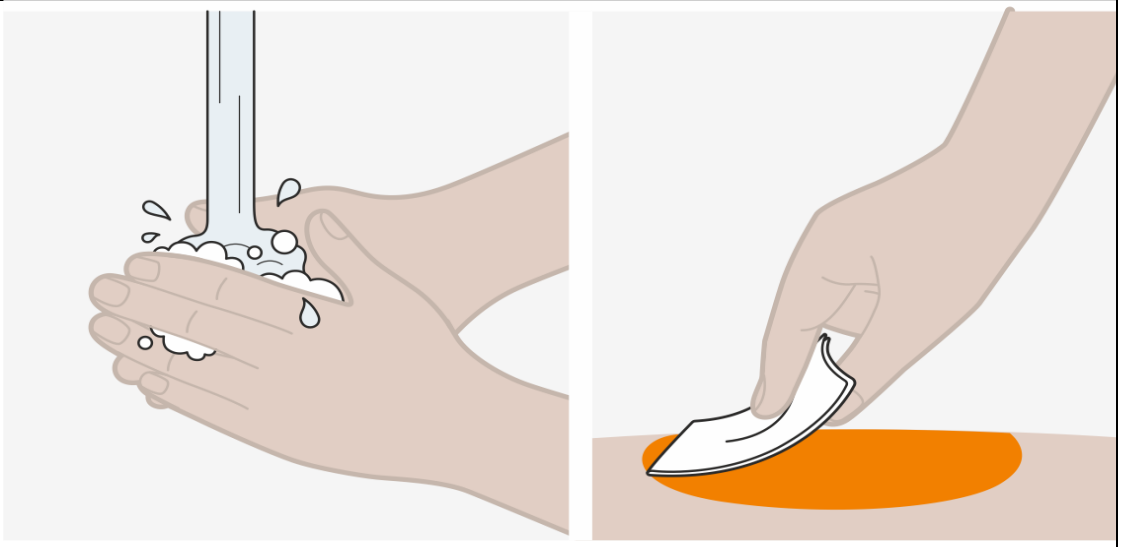
4. Choose your injection site



- You can inject Nucala into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

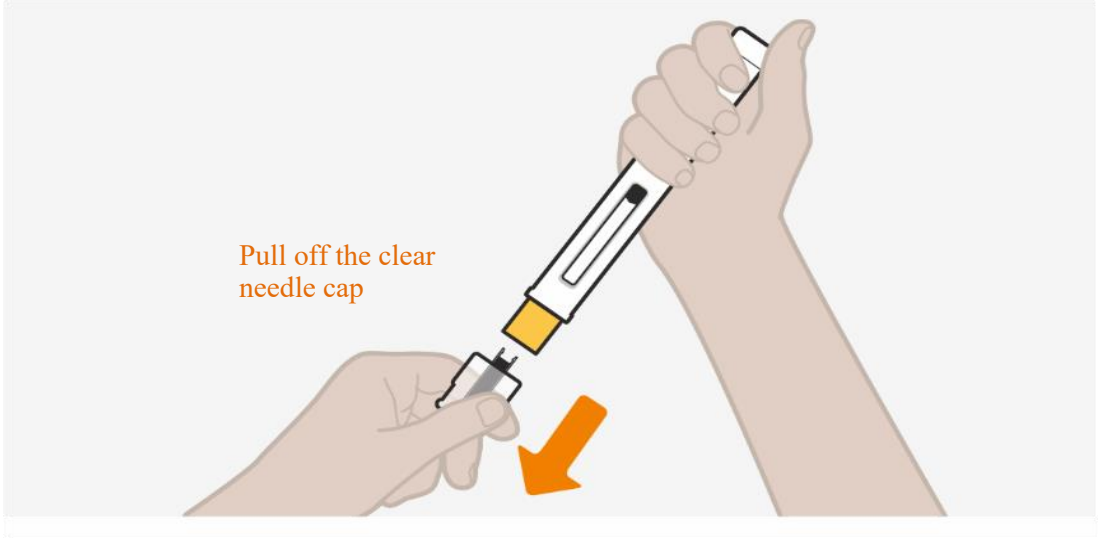


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the clear needle cap

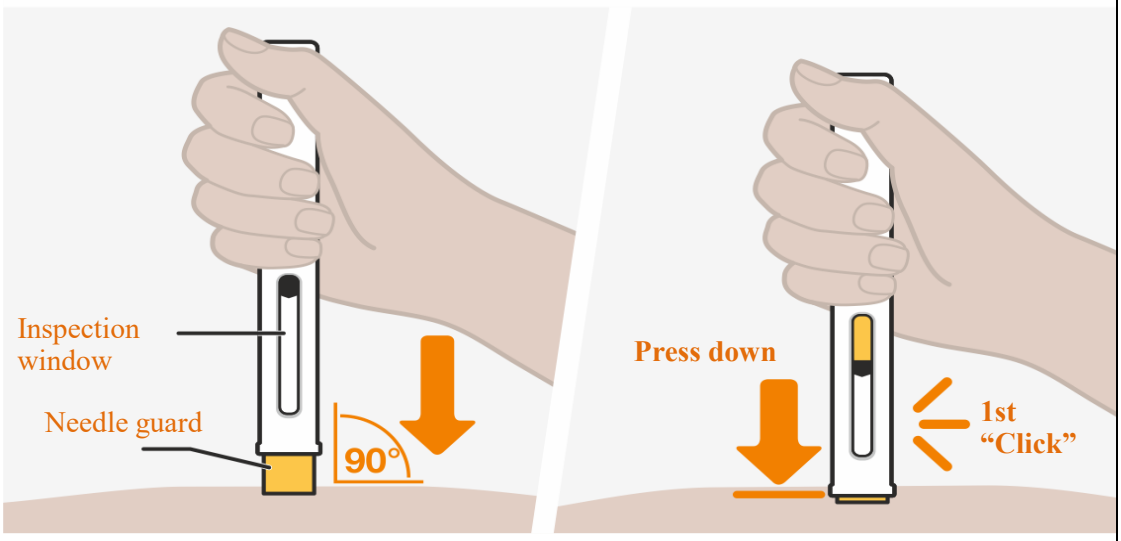


- Remove the clear needle cap from the pen by firmly pulling it straight off.
- Do not worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not touch the yellow needle guard with your fingers. This could activate the pen too soon and may cause a needle injury.

After removal, **do not** put the needle cap back onto the pen, as it may accidentally start the injection.

7. Start your injection

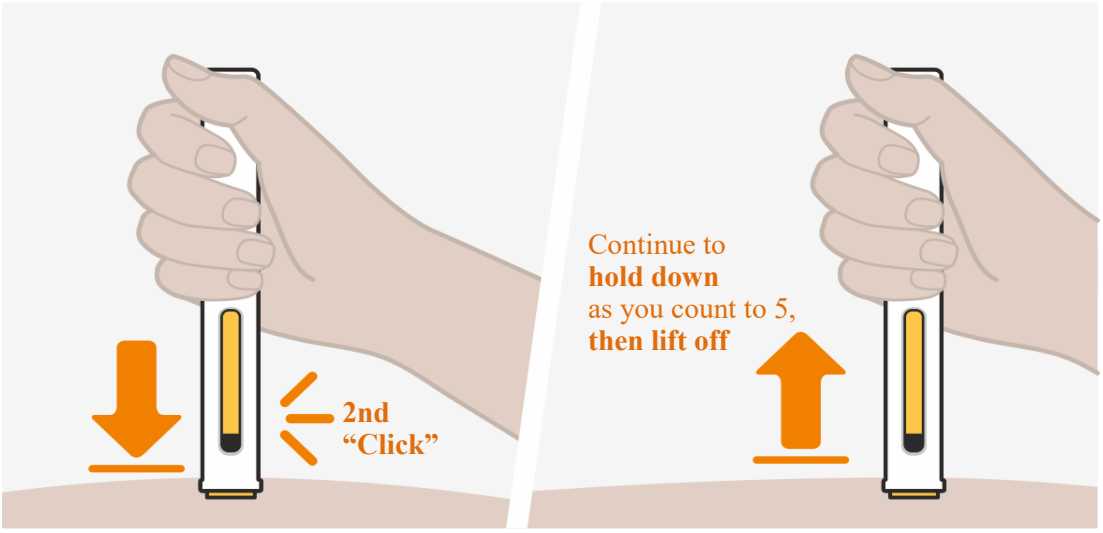


- Hold the pen with its inspection window facing towards you, so you can see it, and with the yellow needle guard facing down.
- Place the pen straight onto your injection site with the yellow needle guard flat against the surface of your skin, as shown.
- To start your injection, push the pen down all the way and keep it held down against your skin. The yellow needle guard will slide up into the pen.
- You should hear the 1st "click" to tell you your injection has started.
- The yellow indicator will move down through the inspection window as you receive your dose.

Do not lift the pen from your skin at this stage, as that may mean you don't get your full dose of medicine. Your injection may take up to 15 seconds to complete.

Do not use the pen if the yellow needle guard doesn't slide up as described. Dispose of it (see Step 9), and start again with a new pen.

8. Hold the pen in place to complete your injection



- Continue to hold the pen down until you hear the 2nd "click", and the stopper and yellow indicator have stopped moving and fill the inspection window.
- Continue to hold the pen in place while you count to 5. Then lift the pen away from your skin.
- If you do **not** hear the 2nd "click":
  - –Check that the inspection window is filled with the yellow indicator.
  - –If you are not sure, hold the pen down for another 15 seconds to make sure the injection is complete.

Do not lift the pen until you are sure you have completed your injection.

- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.

Do not rub your injection site.

Dispose

9. Dispose of the used pen

- Dispose of the used pen and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used pens and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 100 mg solution for injection in pre-filled syringe

mepolizumab

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.
- 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 Nucala is and what it is used for
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

Mepolizumab, the active substance in Nucala, blocks a protein called *interleukin-5*. By blocking the action of this protein*,* it limits the production of eosinophils from the bone marrow and lowers the number of eosinophils in the bloodstream and the lungs.

Severe eosinophilic asthma

Some people with severe asthma have too many *eosinophils* (a type of white blood cell) in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma Nucala can treat.

Nucala can reduce your number of asthma attacks, if you or your child are already using medicines such as high dose inhalers, but your asthma is not well controlled by these medicines.
If you are taking medicines called *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your asthma.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood, and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps.

Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of white blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin**.**
Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

2. What you need to know before you use Nucala

Do not use Nucala:
- if you are **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

➔ **Tell your doctor or nurse** if your asthma remains uncontrolled, or gets worse, after you start Nucala treatment.

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body (see section 4, 'Possible side effects').
If you may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you are given Nucala.

Parasitic infections
Nucala may weaken your resistance to infections caused by parasites. If you already have a parasitic infection; it should be treated before you start treatment with Nucala. If you live in a region where these infections are common or if you are travelling to such a region:

➔ **Check with your doctor** if you think any of these may apply to you.

Children and adolescents

Severe eosinophilic asthma

The pre-filled syringe is not intended for use in **children below 12 years of age** for the treatment of severe eosinophilic asthma.
For children aged 6-11 years, contact your doctor who will prescribe the recommended dose of Nucala which will be administered by a nurse or doctor.

CRSwNP

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

EGPA

This medicine is not intended for use in **children below 6 years of age** for the treatment of EGPA.

HES

This medicine is not intended for use in **adolescents or children below 18 years of age** for the treatment of HES.

Other medicines and Nucala
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma, CRSwNP, EGPA or HES

- **Don't suddenly stop taking** your existing medicines for your asthma, CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Nucala.

Pregnancy and breast-feeding
If you are pregnant, if you think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use Nucala.

Driving and using machines
The possible side effects of Nucala are unlikely to affect your ability to drive or use machines.

Nucala contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you or your caregiver can inject Nucala. If appropriate, they will then provide training to show you or your caregiver the correct way to use Nucala.

Nucala must be given to children aged 6 to 11 years by a doctor, nurse or trained caregiver.

Severe eosinophilic asthma

The recommended dose for adults and adolescents aged 12 years and older is 100 mg. You will have 1 injection every four weeks.

CRSwNP

The recommended dose for adults is 100 mg. You will have 1 injection every four weeks.

EGPA

The recommended dose for adults and adolescents aged 12 years and older is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:
The recommended dose is 200 mg. You will have 2 injections every four weeks.

Children weighing less than 40 kg:
The recommended dose is 100 mg. You will have 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

The recommended dose for adults is 300 mg. You will have 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

Instructions for using the pre-filled syringe are given on the other side of this leaflet.

If you use more Nucala than you should
If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed
You or your caregiver should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time for your next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala
Do not stop injections of Nucala unless your doctor advises you to. Interrupting or stopping the treatment with Nucala may cause your symptoms and attacks to come back.

If your symptoms get worse while receiving injections of Nucala:

➔ Call your doctor

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. The side effects caused by Nucala are usually mild to moderate but can occasionally be serious.

Allergic reactions
Some people may have allergic or allergic-like reactions. These reactions may be common (they can affect **up to 1 in 10 people).** They usually occur within minutes to hours after the injection, but sometimes symptoms can start up to several days later.

Symptoms can include:
- chest tightness, cough, difficulty breathing
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- swelling of eyelids, face, lips, tongue or mouth
- hives
- rash

➔ **Seek medical attention immediately** if you think you (or your child) may be having a reaction.

If you may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you (or your child) are given Nucala

Other side effects include:

Very common:
may affect more than 1 in 10 people
- headache

Common:
may affect up to 1 in 10 people
- chest infection - symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare:
may affect up to 1 in 1 000 people
- Severe allergic reactions (*anaphylaxis*)

➔ **Tell your doctor or a nurse immediately** if you get any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor 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 Nucala

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

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

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

The Nucala pre-filled syringe can be removed from the refrigerator and kept in its unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

6. Contents of the pack and other information

What Nucala contains
The active substance is mepolizumab.

Each 1 mL pre-filled syringe contains 100 mg of mepolizumab.
The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 1 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled syringe.

Nucala is available in a pack containing 1 pre-filled syringe or in multipacks comprised of 3 x 1 pre-filled syringes or 9 x 1 pre-filled syringes.

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Manufacturer
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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 web site: http://www.ema.europa.eu

7. Step by step instructions for using the 100 mg pre-filled syringe

Administer once every four weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. Nucala pre-filled syringe is for use **under the skin only** (subcutaneous).

How to store Nucala

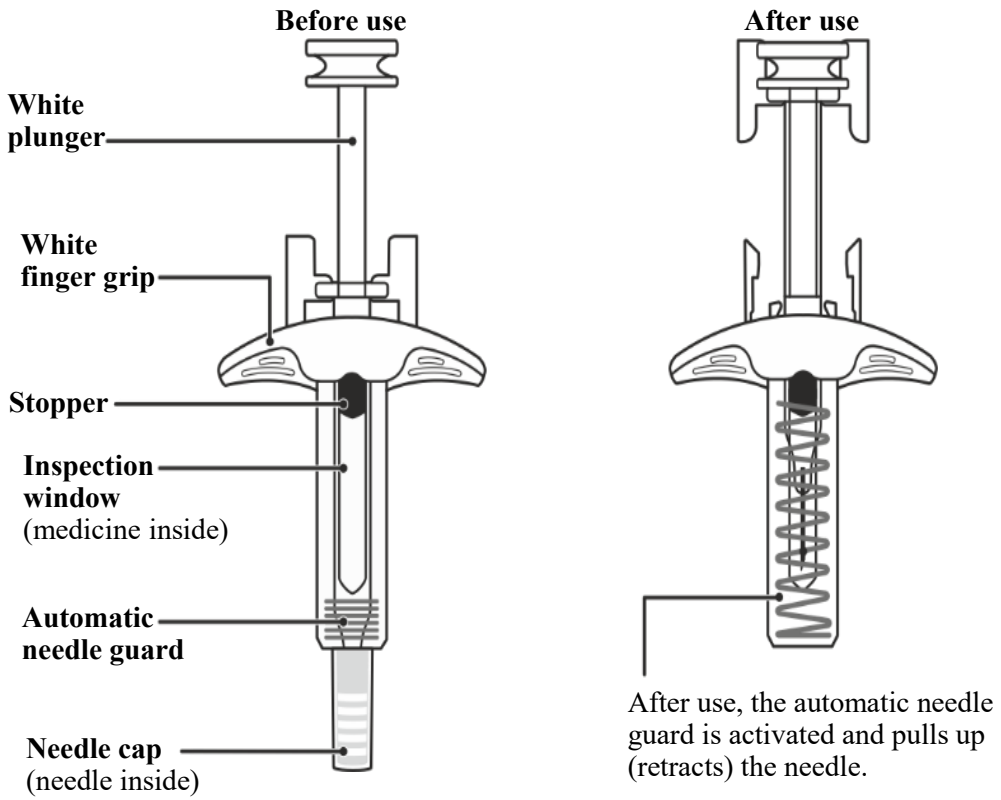
- Keep refrigerated before use.
- Do not freeze.
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled syringe away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use Nucala

The pre-filled syringe should be used only once and then discarded.

- **Do not** share your Nucala pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled syringe



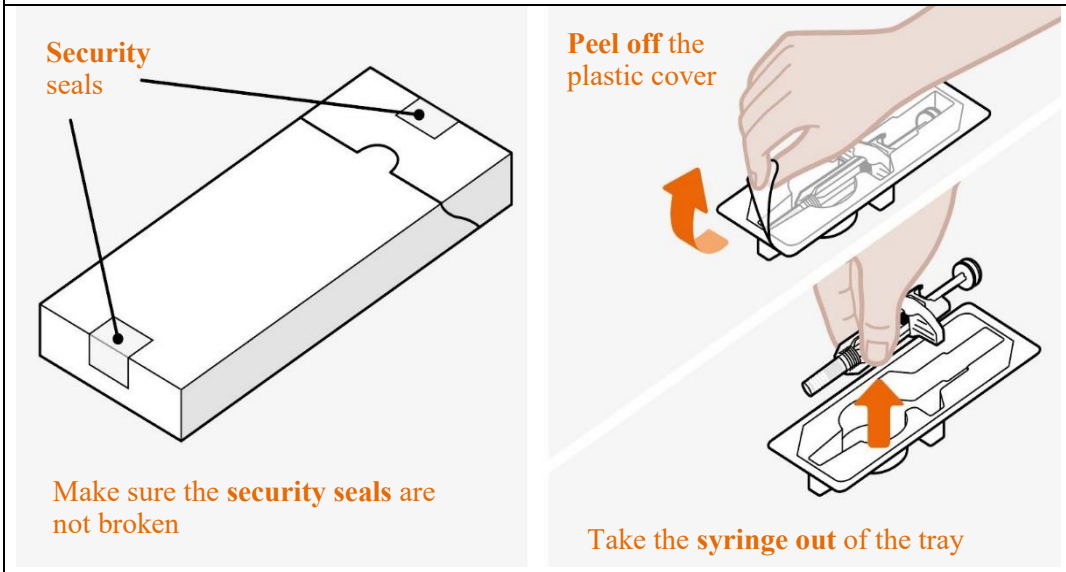
Prepare

1. Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled syringe
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

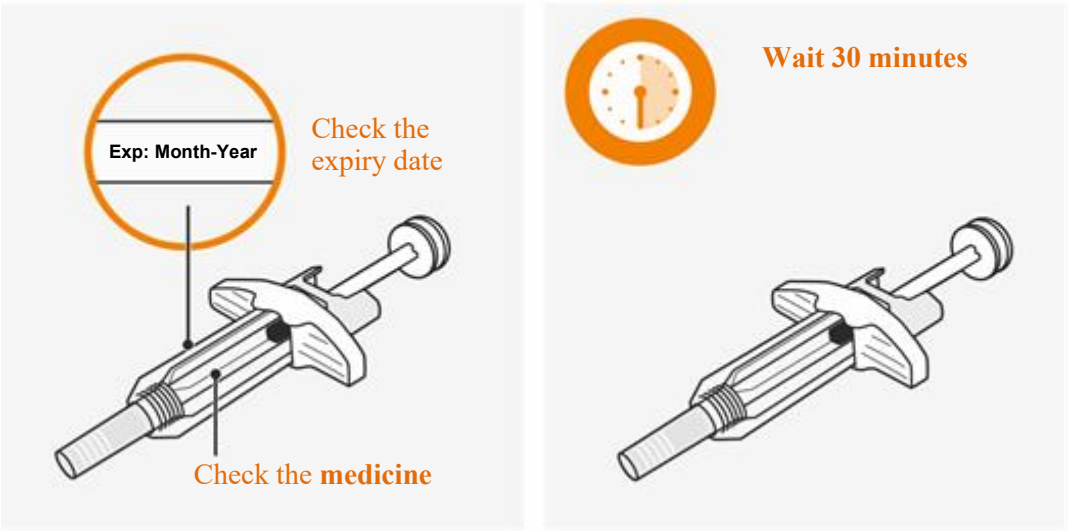
2. Take out your pre-filled syringe



- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.
Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use

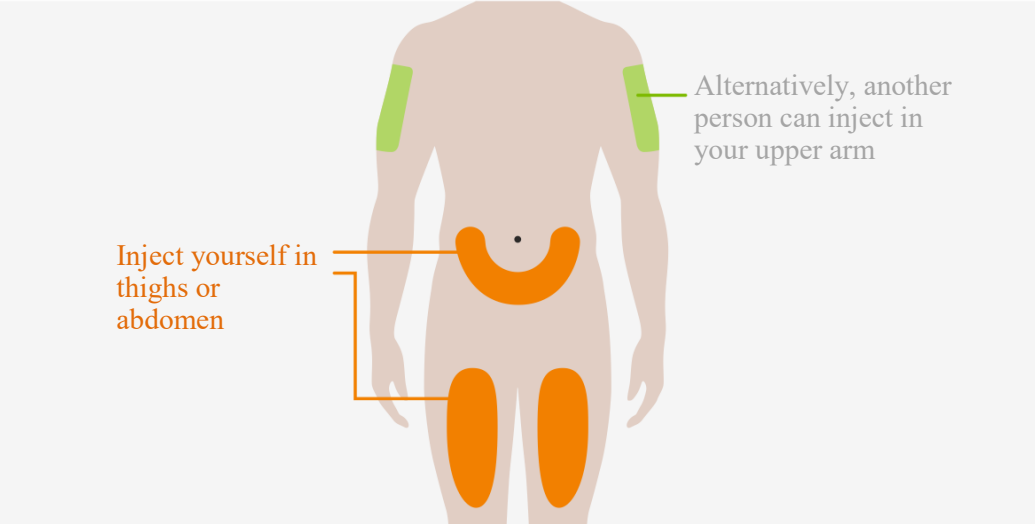


- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.

- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the syringe in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the syringe if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step

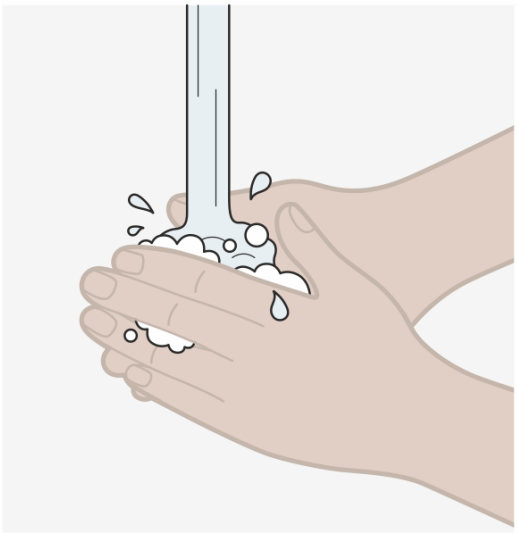
4. Choose your injection site

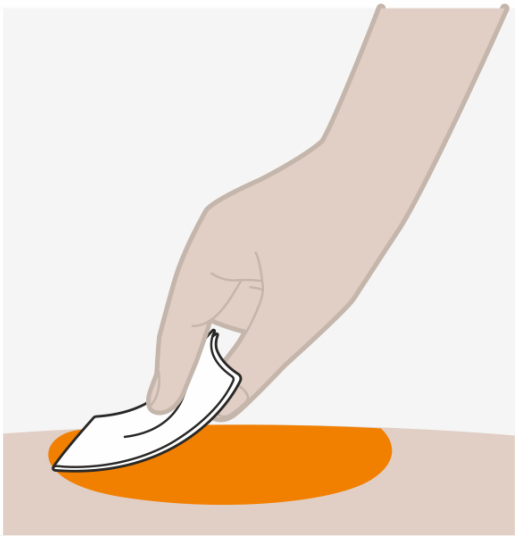


- You can inject Nucala into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site



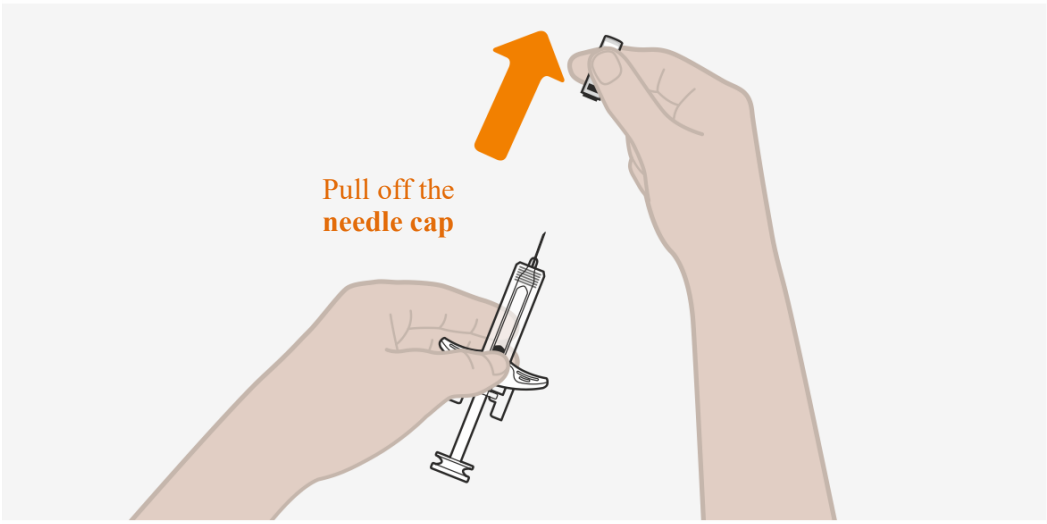


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not let the needle touch any surface.

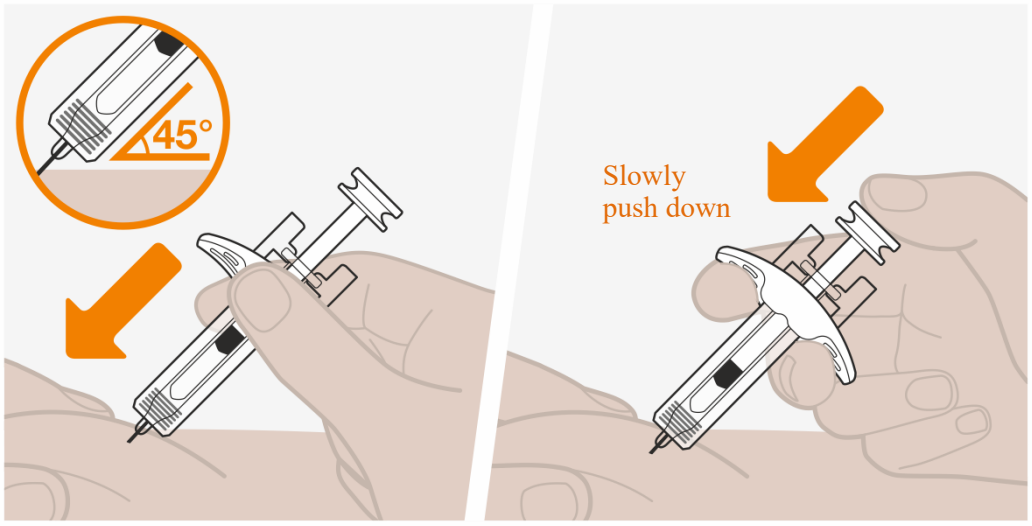
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not receive your full dose.

Do not expel any air bubbles from the syringe.

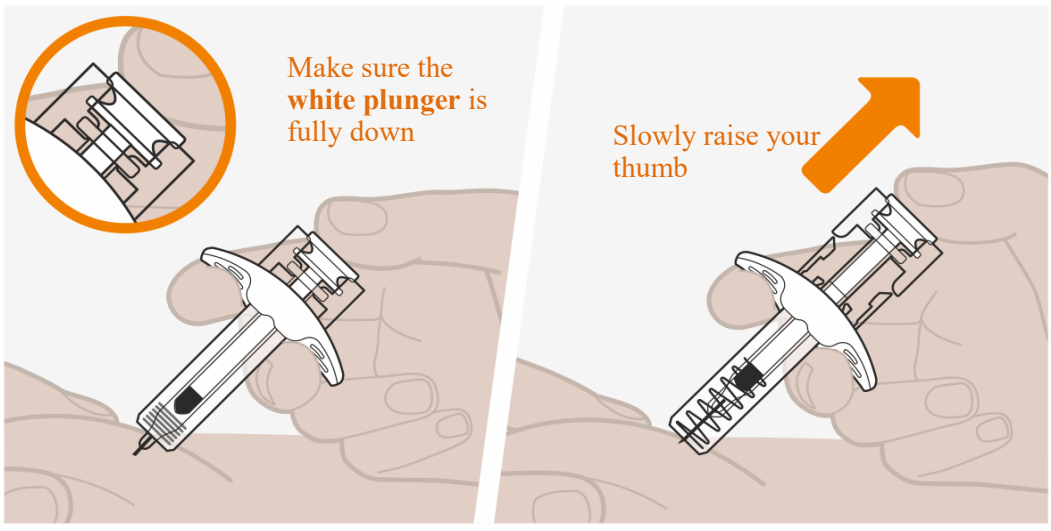
Do not put the needle cap back onto the syringe. This could cause a needle injury.

7. Start your injection



- Use your free hand to pinch the skin around your injection site. Keep the skin pinched throughout your injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject your full dose.

8. Complete your injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub your injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used syringes and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 40 mg solution for injection in pre-filled syringe

mepolizumab

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 a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of the child you are caring for.
- If the child gets 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 Nucala is and what it is used for
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** in adults, adolescents and children aged 6 years and older.

Some people with severe asthma have too many *eosinophils* (a type of white blood cell) in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma Nucala can treat.

Nucala can reduce the number of asthma attacks, if the child is already using medicines such as high dose inhalers, but their asthma is not well controlled by these medicines.
If the child is taking medicines called *oral corticosteroids,* Nucala can also help reduce the daily dose they need to control their asthma.

Mepolizumab, the active substance in Nucala, blocks a protein called *interleukin-5*. By blocking the action of this protein*,* it limits the production of eosinophils from the bone marrow and lowers the number of eosinophils in the bloodstream and the lungs.

2. What you need to know before you use Nucala

Do not use Nucala:
- if the child you are caring for is **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

  ➔ **Check with your doctor** if you think this applies to the child.

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

➔ **Tell your doctor or nurse** if the child's asthma remains uncontrolled, or gets worse, after starting Nucala treatment.

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body (see section 4, 'Possible side effects').

If the child may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you give Nucala.

Parasitic infections
Nucala may weaken the child's resistance to infections caused by parasites. If they already have a parasitic infection; it should be treated before they start treatment with Nucala. If they live in a region where these infections are common or if they are travelling to such a region:

➔ **Check with your doctor** if you think any of these may apply to the child.

Children and adolescents
This medicine is not intended for use in **children below 6 years of age.**

Other medicines and Nucala
Tell your doctor if the child is taking, has recently taken or might take any other medicines.

Other medicines for asthma

✘ **Don't suddenly stop giving** the child's preventer medicines for their asthma once they have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on their response to Nucala.

Pregnancy and breast-feeding
Patients who are pregnant, think they may be pregnant or are planning to have a baby, must **ask their doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **Patients who are breast-feeding must check with their doctor** before using Nucala.

Driving and using machines
The possible side effects of Nucala are unlikely to affect the ability to drive or use machines.

Nucala contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 40 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you can inject Nucala for the child you are caring for. If appropriate, they will then provide training to show you the correct way to use Nucala.

The recommended dose for children aged 6 to 11 years old is 40 mg. You will give 1 injection every four weeks.

Instructions for using the pre-filled syringe are given on the other side of this leaflet.

If you use more Nucala than you should
If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed
You should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time to give the next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala
Do not stop injections of Nucala unless your doctor advises you to. Interrupting or stopping the treatment with Nucala may cause the child's asthma symptoms and attacks to come back.

If the child's asthma symptoms get worse while receiving injections of Nucala:

➔ Call your doctor

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. The side effects caused by Nucala are usually mild to moderate but can occasionally be serious.

Allergic reactions
Some people may have allergic or allergic-like reactions. These reactions may be common (they can affect **up to 1 in 10 people).** They usually occur within minutes to hours after the injection, but sometimes symptoms can start up to several days later.

Symptoms can include:
- chest tightness, cough, difficulty breathing
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- swelling of eyelids, face, lips, tongue or mouth
- hives
- rash

➔ **Seek medical attention immediately** if you think the child may be having a reaction.

If the child may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before the child is given Nucala

Other side effects include:

Very common: may affect more than 1 in 10 people
- headache

Common: may affect up to 1 in 10 people
- chest infection - symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare:
may affect up to 1 in 1 000 people
- Severe allergic reactions (*anaphylaxis*)

➔ **Tell your doctor or a nurse immediately** if the child gets any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor 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 Nucala

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

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

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

The Nucala pre-filled syringe can be removed from the refrigerator and kept in its unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

6. Contents of the pack and other information

What Nucala contains
The active substance is mepolizumab.

Each 0.4 mL pre-filled syringe contains 40 mg of mepolizumab.
The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 0.4 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled syringe.

Nucala is available in a pack containing 1 pre-filled syringe or in multipacks comprised of 3 x 1 pre-filled syringes.

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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 web site: http://www.ema.europa.eu

7. Step by step instructions for using the 40 mg pre-filled syringe

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. Nucala pre-filled syringe is for **use under the skin only** (subcutaneous).

How to store Nucala

- Keep refrigerated before use.
- Do not freeze
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled syringe away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

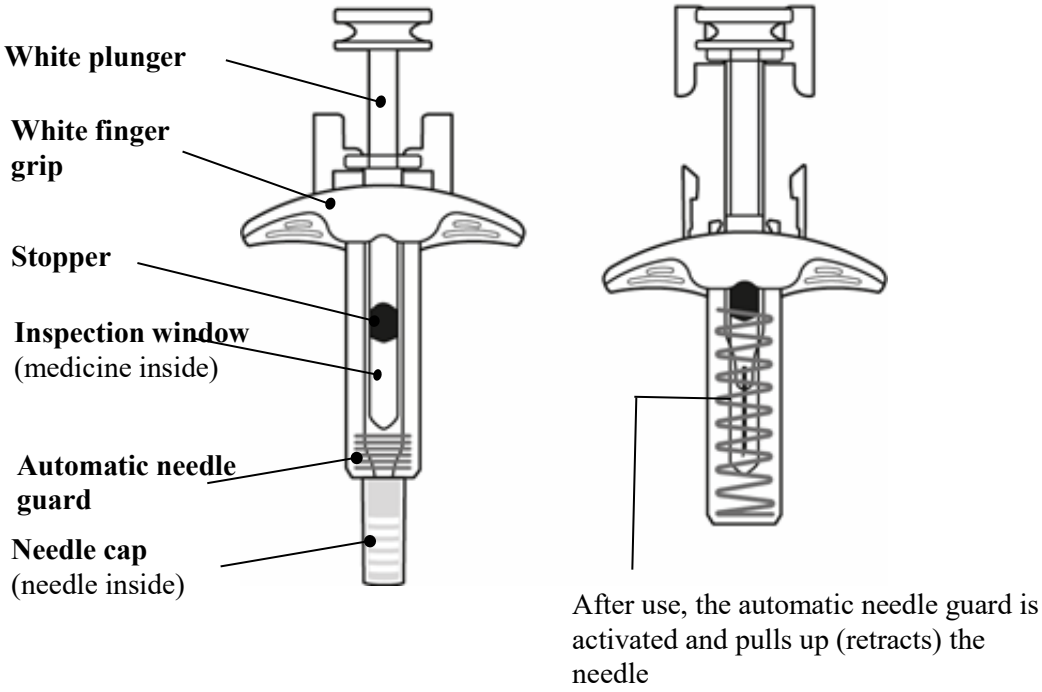
Before you use Nucala

The pre-filled syringe should be used only once and then discarded.

- **Do not** share the Nucala pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before the injection.

Know the pre-filled syringe

Before Use **After Use**



After use, the automatic needle guard is activated and pulls up (retracts) the needle

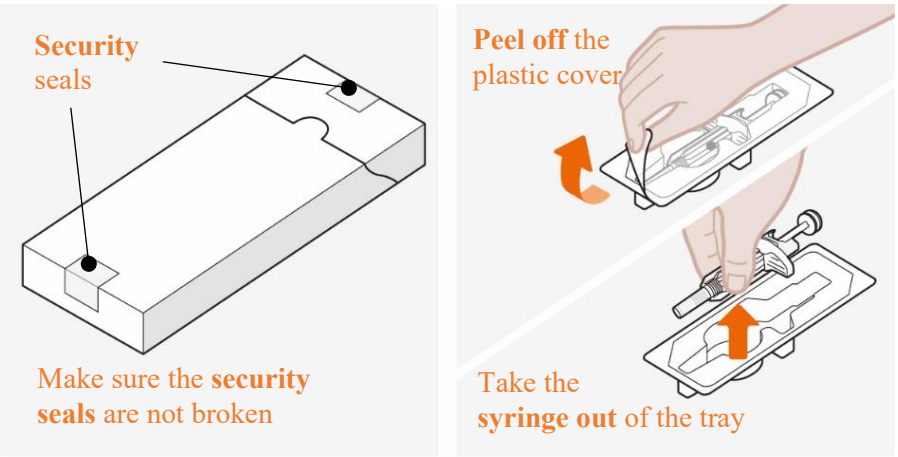
Prepare

1. Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled syringe
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

2. Take out the pre-filled syringe

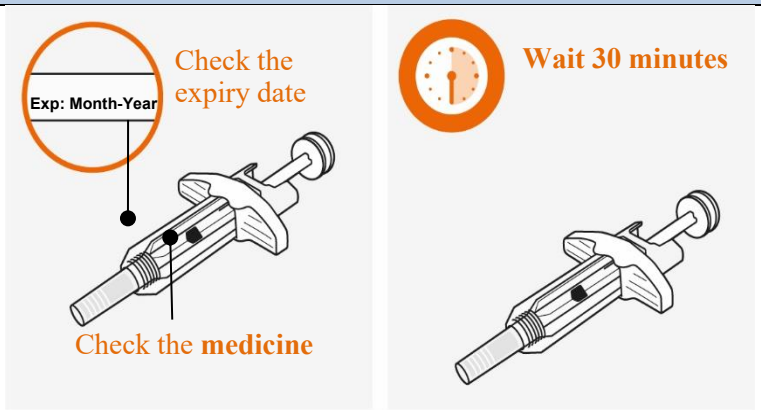


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

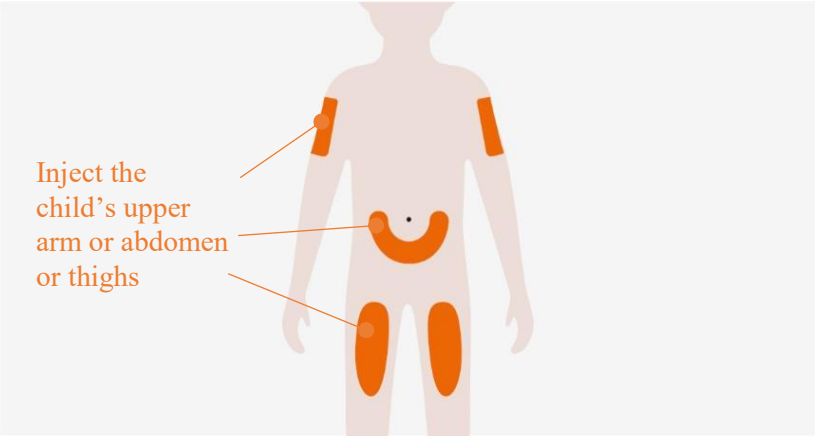
3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the syringe in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the syringe if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step.

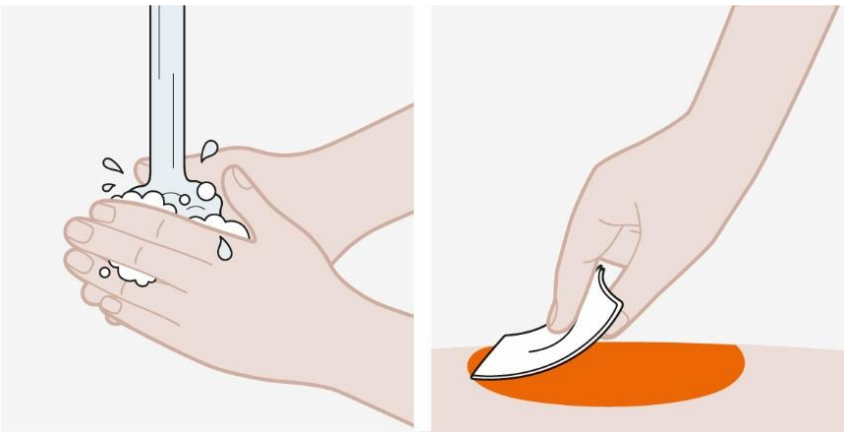
4. Choose the injection site



- You can inject Nucala into the upper arm, abdomen or thigh of the child you are caring for.

Do not inject where the skin is bruised, tender, red or hard.
Do not inject within 5 cm of the navel (belly button).

5. Clean the injection site



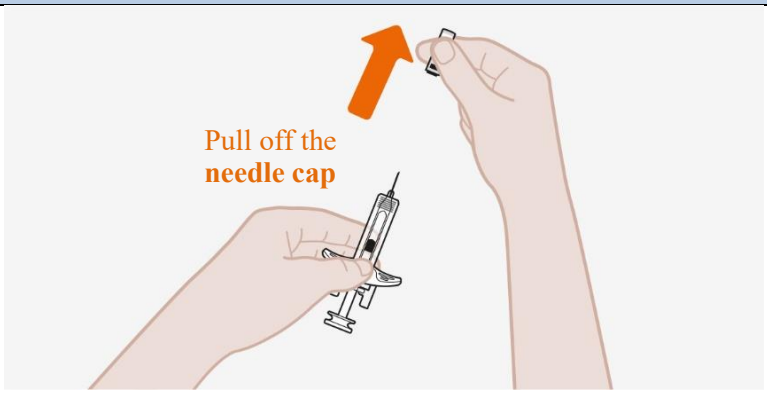
- Wash your hands with soap and water.

- Clean the injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch the cleaned injection site again until you have finished the injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not let the needle touch any surface.

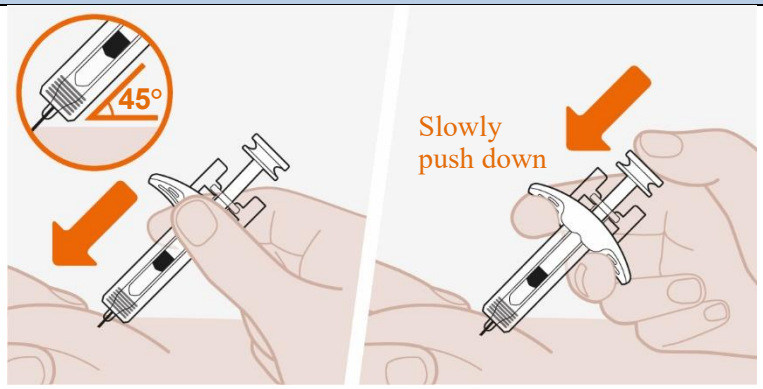
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not give the full dose.

Do not expel any air bubbles from the syringe.

Do not put the needle cap back onto the syringe. This could cause a needle injury.

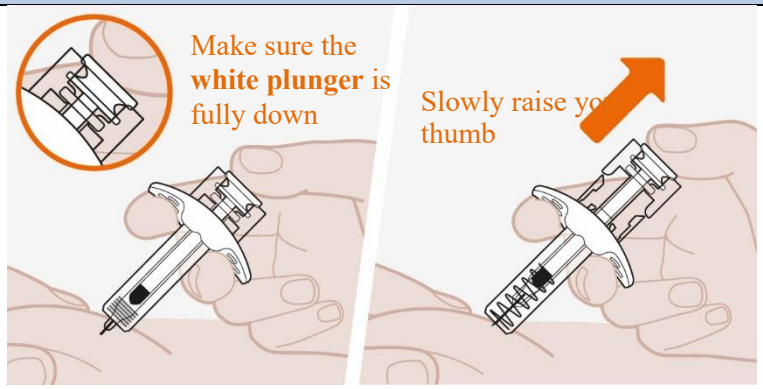
7. Start the injection



- Use your free hand to pinch the skin around the injection site. Keep the skin pinched throughout the injection.

- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject the full dose.

8. Complete the injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub the injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep the used syringes and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 100 mg powder for solution for injection
mepolizumab

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.
- 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 Nucala is and what it is used for
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

Mepolizumab, the active substance in Nucala, blocks a protein called *interleukin-5*. By blocking the action of this protein, it limits the production of eosinophils from the bone marrow and lowers the number of eosinophils in the bloodstream and the lungs.

Severe eosinophilic asthma
Some people with severe asthma have too many *eosinophils* (a type of white blood cell) in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma Nucala can treat.

Nucala can reduce your number of asthma attacks, if you or your child are already using medicines such as high dose inhalers, but your asthma is not well controlled by these medicines.
If you are taking medicines called *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your asthma.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps.
Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of white blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin**.**
Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids,* Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

2. What you need to know before you use Nucala

Do not use Nucala:
- if you are **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

  ➔ **Check with your doctor** if you think this applies to you.

Warnings and precautions
Talk to your doctor before using this medicine.

Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

➔ **Tell your doctor or nurse** if your asthma remains uncontrolled, or gets worse, after you start Nucala treatment.

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body (see section 4, 'Possible side effects').

If you may have had a similar reaction to any injection or medicine,

➔ **Tell your doctor before you are given Nucala**.

Parasitic infections
Nucala may weaken your resistance to infections caused by parasites. If you already have a parasitic infection; it should be treated before you start treatment with Nucala. If you live in a region where these infections are common or if you are travelling to such a region:

➔ **Check with your doctor** if you think any of these may apply to you.

Children

Severe eosinophilic asthma and EGPA

This medicine is not intended for use in **children below 6 years of age** for the treatment of severe eosinophilic asthma or EGPA.

CRSwNP and HES

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP or HES.

Other medicines and Nucala
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma,CRSwNP, EGPA or HES

- **Don't suddenly stop taking** your existing medicines for your asthma,CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on your response to Nucala.

Pregnancy and breast-feeding
If you are pregnant, if you think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use Nucala.

Driving and using machines
The possible side effects of Nucala are unlikely to affect your ability to drive or use machines.

Nucala contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given to you by a doctor, nurse or healthcare professional, as an injection just under the skin (subcutaneously).

Severe eosinophilic asthma

Adults and adolescents aged 12 years and over
The recommended dose for adults and adolescents is 100 mg. You will be given 1 injection every four weeks.

Children aged 6 to 11 years old
The recommended dose is 40 mg. You will be given 1 injection every four weeks.

CRSwNP

Adults
The recommended dose for adults is 100 mg. You will be given 1 injection every four weeks.

EGPA

Adults and adolescents aged 12 years and over
The recommended dose for adults and adolescents is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:
The recommended dose is 200 mg. You will be given 2 injections every four weeks.

Children weighing less than 40 kg:
The recommended dose is 100 mg. You will be given 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

Adults
The recommended dose for adults is 300 mg. You will be given 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

If a dose of Nucala is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Stopping treatment with Nucala
Do not stop receiving injections of Nucala unless your doctor advises you to. Interrupting or stopping the treatment with Nucala may cause your symptoms and attacks to come back.

If your symptoms get worse while receiving injections of Nucala
➔ Call your doctor.

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. The side effects caused by Nucala are usually mild to moderate but can occasionally be serious.

Allergic reactions
Some people may have allergic or allergic-like reactions. These reactions may be common (they can affect **up to 1 in 10 people).** They usually occur within minutes to hours after the injection, but sometimes symptoms can start up to several days later.

Symptoms can include:
- chest tightness, cough, difficulty breathing

- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- swelling of eyelids, face, lips, tongue or mouth
- hives
- rash

➔ **Seek medical attention immediately** if you think you (or your child) may be having a reaction.

If you (or your child) may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you are given Nucala.

Other side effects include:

Very common:
may affect more than 1 in 10 people
- headache

Common:
may affect up to 1 in 10 people
- chest infection - symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare:
may affect up to 1 in 1 000 people
- Severe allergic reactions (*anaphylaxis*)

➔ **Tell your doctor or a nurse immediately** if you get any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor 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 Nucala

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

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

Store below 25°C.
Do not freeze.
Store in the original package to protect from light.

6. Contents of the pack and other information

What Nucala contains
The active substance is mepolizumab. Each vial contains 100 mg of mepolizumab.
After reconstitution, each ml of solution contains 100 mg mepolizumab.

The other ingredients are sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80.

What Nucala looks like and contents of the pack

Nucala is a lyophilised white powder supplied in a clear, colourless glass vial with a rubber stopper.

Nucala is available in a pack containing 1 vial, or in multipacks with 3 individual vials.

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Manufacturer
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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 web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

7. Step-by-step instructions for use and handling, reconstitution, and administration

Nucala is provided as a lyophilised, white powder in a single-use vial for subcutaneous injection only. Reconstitution should be carried out under aseptic conditions.

Once reconstituted, Nucala will contain a concentration of 100 mg/mL mepolizumab. The solution for injection can be stored between 2°C to 30°C for no more than 8 hours. Any unused concentrate or solution remaining after 8 hours must be discarded.

Traceability

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

Instructions for reconstitution for each vial

1. **Reconstitute the contents of the vial with 1.2 mL of sterile water for injections** preferably using a 2 to 3 ml syringe and a 21 gauge needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

   *Note: The reconstituted solution **must not be shaken** during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the sterile water has been added, but it may take additional time.*

2. If a mechanical reconstitution device (swirler) is used to reconstitute Nucala, reconstitution can be accomplished by swirling at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1 000 rpm for no longer than 5 minutes is acceptable.
3. Following reconstitution, Nucala should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be used.
4. The reconstituted solution, if not used immediately must be:
   - Protected from sunlight
   - Stored below 30°C, not frozen
   - Discarded if not used within 8 hours of reconstitution

Instructions for administration of 100 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 1 mL of reconstituted Nucala from one vial. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

If more than one vial is required for administration of the prescribed dosage, repeat steps 1 to 3. It is recommended that individual injection sites are separated by at least 5 cm.

Instructions for administration of 40 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 0.4mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation. Dispose of the remaining solution.
3. Administer the 0.4mL injection (equivalent to 40 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Disposal

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

GLOBAL DATASHEET

Mepolizumab

※2～65頁を削除

1.7. 同種同効品一覧表

同種同効品として、デュピクセント皮下注 300 mg シリンジ、同皮下注 300 mg ペン及び同皮下注 200 mg シリンジを本剤と対比して 表 1.7.1 に示す。

表 1.7.1 同種同効品一覧表

販　売　名	ヌーカラ皮下注 100 mg シリンジ ヌーカラ皮下注 100 mg ペン	デュピクセント皮下注 300 mg シリンジ デュピクセント皮下注 300 mg ペン デュピクセント皮下注 200 mg シリンジ
一　般　名	メポリズマブ（遺伝子組換え）	デュピルマブ（遺伝子組換え）
会　社　名	グラクソ・スミスクライン株式会社	サノフィ株式会社
効能又は効果	気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る） 既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症 鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る） （下線部追加）	300 mg シリンジ、300 mg ペン 既存治療で効果不十分な下記皮膚疾患 　アトピー性皮膚炎 　結節性痒疹 　特発性の慢性蕁麻疹 気管支喘息（既存治療によっても喘息症状をコントロールできない重症又は難治の患者に限る） 鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る） 200 mg シリンジ 既存治療で効果不十分な下記皮膚疾患 　アトピー性皮膚炎 　特発性の慢性蕁麻疹
添付文書改訂日	－	2024 年 2 月

＊2024年２月改訂（第８版、効能変更）
2023年12月改訂（第７版）

貯　　法：凍結を避け、２～８℃にて保存
有効期間：36箇月

日本標準商品分類番号
87449

	300mgペン	300mgシリンジ	200mgシリンジ
承認番号	30200AMX00926	23000AMX00015	30500AMX00261
販売開始	2020年11月	2018年４月	2023年12月

DUPIeL04

ヒト型抗ヒトIL-4/13受容体モノクローナル抗体 デュピルマブ（遺伝子組換え）製剤

生物由来製品、劇薬、処方箋医薬品：注意－医師等の処方箋により使用すること

デュピクセント® 皮下注300mgペン
デュピクセント® 皮下注300mgシリンジ
デュピクセント® 皮下注200mgシリンジ

DUPIXENT® S.C. Injection

（一部）最適使用推進ガイドライン対象品目

DUPIXENT® sanofi REGENERON

1. 警告

本剤の投与は、適応疾患の治療に精通している医師のもとで行うこと。

2. 禁忌（次の患者には投与しないこと）

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		デュピクセント皮下注300mgペン	デュピクセント皮下注300mgシリンジ	デュピクセント皮下注200mgシリンジ
成　　分		1製剤（2mL）中の分量	1製剤（2mL）中の分量	1製剤（1.14mL）中の分量
有効成分	デュピルマブ（遺伝子組換え）[注1)]	300mg	300mg	200mg
添加剤	L-ヒスチジン	5.4mg	5.4mg	3.10mg
	L-ヒスチジン塩酸塩水和物	1.0mg	1.0mg	0.60mg
	L-アルギニン塩酸塩	10.5mg	10.5mg	12.01mg
	酢酸ナトリウム水和物	2.6mg	2.6mg	1.50mg
	氷酢酸	0.3mg	0.3mg	0.19mg
	精製白糖	100mg	100mg	57.00mg
	ポリソルベート80	4mg	4mg	2.28mg

注1）本剤は遺伝子組換え技術により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	デュピクセント皮下注300mgペン	デュピクセント皮下注300mgシリンジ	デュピクセント皮下注200mgシリンジ
性状・剤形	無色～微黄色の澄明又はわずかに乳白光を呈する液（注射剤）		
pH	5.6～6.2		
浸透圧比	約1.0（生理食塩液に対する比）		

＊4. 効能又は効果

300mgペン、300mgシリンジ
既存治療で効果不十分な下記皮膚疾患
- **○アトピー性皮膚炎**[注)]
- **○結節性痒疹**
- **○特発性の慢性蕁麻疹**
- **○気管支喘息（既存治療によっても喘息症状をコントロールできない重症又は難治の患者に限る）**[注)]
- **○鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）**[注)]

200mgシリンジ
既存治療で効果不十分な下記皮膚疾患
- **○アトピー性皮膚炎**[注)]
- **○特発性の慢性蕁麻疹**

注）最適使用推進ガイドライン対象

5. 効能又は効果に関連する注意

〈アトピー性皮膚炎〉

5.1 ステロイド外用剤やタクロリムス外用剤等の抗炎症外用剤による適切な治療を一定期間施行しても、十分な効果が得られず、強い炎症を伴う皮疹が広範囲に及ぶ患者に用いること。［17.1.1-17.1.3 参照］

5.2 原則として、本剤投与時にはアトピー性皮膚炎の病変部位の状態に応じて抗炎症外用剤を併用すること。

5.3 本剤投与時も保湿外用剤を継続使用すること。

〈結節性痒疹〉

5.4「17. 臨床成績」の項の内容を熟知し、臨床試験に組み入れられた患者の背景を十分に理解した上で、本剤はステロイド外用剤等による治療を施行しても、痒疹結節を主体とする病変が多発し、複数の部位に及ぶ患者に用いること。［17.1.4 参照］

5.5 最新の診療ガイドライン等を参考に、臨床症状及び全身検索に基づいて他の皮膚疾患との鑑別を行うこと。

〈特発性の慢性蕁麻疹〉

＊5.6 食物、物理的刺激等の蕁麻疹の症状を誘発する原因が特定されず、ヒスタミンH_1受容体拮抗薬の増量等の適切な治療を行っても、日常生活に支障をきたすほどの痒みを伴う膨疹が繰り返して継続的に認められる場合に本剤を追加して投与すること。［17.1.5 参照］

〈気管支喘息〉

5.7 最新のガイドライン等を参考に、中用量又は高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。

5.8 本剤はIL-4及びIL-13シグナル伝達を阻害することにより、喘息の病態に関与する２型炎症反応を抑制することから、臨床試験で認められた本剤投与前の２型炎症に関連するバイオマーカー（血中好酸球数、FeNO、IgE等）の値と有効性の関係を十分に理解し、患者の当該バイオマーカーの値を考慮した上で、適応患者の選択を行うこと。［17.1.6 参照］

5.9 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。

〈鼻茸を伴う慢性副鼻腔炎〉

5.10 本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。

＊6. 用法及び用量

〈アトピー性皮膚炎〉

通常、成人にはデュピルマブ（遺伝子組換え）として初回に600mgを皮下投与し、その後は1回300mgを2週間隔で皮下投与する。

通常、生後6カ月以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

5kg以上15kg未満：1回200mgを4週間隔

15kg以上30kg未満：1回300mgを4週間隔

30kg以上60kg未満：初回に400mg、その後は1回200mgを2週間隔

60kg以上：初回に600mg、その後は1回300mgを2週間隔

〈結節性痒疹〉

通常、成人にはデュピルマブ（遺伝子組換え）として初回に600mgを皮下投与し、その後は1回300mgを2週間隔で皮下投与する。

〈特発性の慢性蕁麻疹〉

通常、成人にはデュピルマブ（遺伝子組換え）として初回に600mgを皮下投与し、その後は1回300mgを2週間隔で皮下投与する。

通常、12歳以上の小児にはデュピルマブ（遺伝子組換え）として体重に応じて以下を皮下投与する。

30kg以上60kg未満：初回に400mg、その後は1回200mgを2週間隔

60kg以上：初回に600mg、その後は1回300mgを2週間隔

〈気管支喘息〉

通常、成人及び12歳以上の小児にはデュピルマブ（遺伝子組換え）として初回に600mgを皮下投与し、その後は1回300mgを2週間隔で皮下投与する。

〈鼻茸を伴う慢性副鼻腔炎〉

通常、成人にはデュピルマブ（遺伝子組換え）として1回300mgを2週間隔で皮下投与する。なお、症状安定後には、1回300mgを4週間隔で皮下投与できる。

7. 用法及び用量に関連する注意

〈アトピー性皮膚炎〉

7.1 本剤による治療反応は、通常投与開始から16週までには得られる。16週までに治療反応が得られない場合は、投与中止を考慮すること。

〈アトピー性皮膚炎、特発性の慢性蕁麻疹〉

＊7.2 200mgシリンジと300mgシリンジ又は300mgペンの生物学的同等性試験は実施していないため、600mgを投与する際には200mgシリンジを使用しないこと。

〈特発性の慢性蕁麻疹〉

＊7.3 臨床試験において、本剤の24週以降の使用経験は無いため、24週以降も継続して投与する場合は、患者の状態を考慮し、その必要性を慎重に判断すること。

特に、用法及び用量どおり、24週間使用しても効果が認められない場合には、漫然と投与を続けないよう注意すること。［17.1.5 参照］

8. 重要な基本的注意

〈効能共通〉

8.1 本剤の投与によって合併する他のアレルギー性疾患の症状が変化する可能性があり、当該アレルギー性疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤の投与間隔変更後及び投与中止後の疾患管理も含めて、本剤投与中から、合併するアレルギー性疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

8.2 ショック、アナフィラキシーがあらわれることがあるので、観察を十分に行い、適切に対処できるようにしておくこと。［11.1.1 参照］

8.3 長期ステロイド療法を受けている患者において、本剤投与開始後にステロイド薬を急に中止しないこと。ステロイド薬の減量が必要な場合には、医師の管理下で徐々に行うこと。

8.4 本剤の臨床試験において、好酸球性肺炎及び好酸球性多発血管炎性肉芽腫症の発現が認められている。本剤投与中は、好酸球数の推移、並びに血管炎性皮疹、肺症状の悪化、心臓合併症及びニューロパチー等に注意すること。

8.5 本剤はIL-4及びIL-13の阻害作用により2型免疫応答を抑制する。2型免疫応答は寄生虫感染に対する生体防御機能に関与している可能性がある。患者が本剤投与中に寄生虫感染を起こし、抗寄生虫薬による治療が無効な場合には、寄生虫感染が治癒するまで本剤の投与を一時中止すること。［9.1.1 参照］

8.6 本剤投与中の生ワクチンの接種は、安全性が確認されていないので避けること。

8.7 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督のもとで投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者又はその保護者が理解し、患者自ら又はその保護者が確実に投与できることを確認した上で、医師の管理指導のもとで実施すること。また、適用後、本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止させ、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、本剤投与後に副作用の発現が疑われる場合は、医療機関へ連絡するよう患者又はその保護者に指導を行うこと。使用済みの注射器を再使用しないよう患者又はその保護者に注意を促し、すべての器具の安全な廃棄方法に関する指導の徹底を行うとともに、使用済みの注射器を廃棄する容器を提供すること。

〈アトピー性皮膚炎〉

8.8 本剤が疾病を完治させる薬剤でなく、本剤投与中も保湿外用剤等を併用する必要があることを患者に対して説明し、患者が理解したことを確認したうえで投与すること。

〈気管支喘息〉

8.9 本剤の投与開始後に喘息症状がコントロール不良であったり、悪化した場合には、医師の診療を受けるよう患者に指導すること。

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 寄生虫感染患者

本剤を投与する前に寄生虫感染の治療を行うこと。［8.5 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。本剤はヒトIgG4モノクローナル抗体であり、ヒトIgGは胎盤関門を通過することが知られている。また、本剤のサル相同抗体を妊娠カニクイザルへ投与した場合、胎盤を通過して胎児に移行することが確認されている。

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。本剤のヒト乳汁への移行は不明であるが、本剤はヒトIgG4モノクローナル抗体であり、ヒトIgGは乳汁中に移行することが知られている。

＊9.7 小児等

〈アトピー性皮膚炎〉

低出生体重児、新生児及び生後6カ月未満の乳児を対象とした臨床試験は実施していない。

〈結節性痒疹、鼻茸を伴う慢性副鼻腔炎〉
小児等を対象とした臨床試験は実施していない。
〈特発性の慢性蕁麻疹〉
6歳未満の小児等を対象とした臨床試験は実施していない。臨床試験において、6歳以上12歳未満の小児に対する投与経験は極めて限られている。
〈気管支喘息〉
12歳未満の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
一般的に生理機能（免疫機能等）が低下している。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用
11.1.1 重篤な過敏症
アナフィラキシー（0.1%未満）が報告されている。血圧低下、呼吸困難、意識消失、めまい、嘔気、嘔吐、そう痒感、潮紅、血管性浮腫等があらわれる可能性がある。[8.2 参照]

11.2 その他の副作用

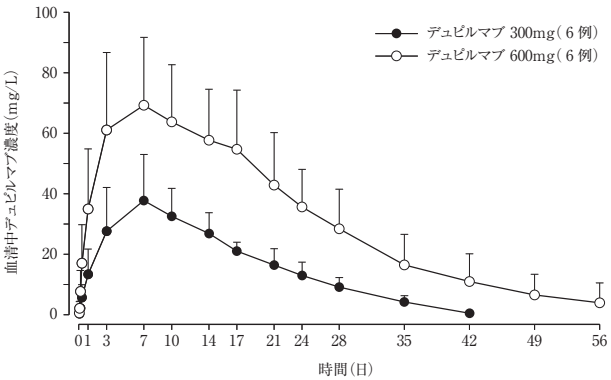
	5%以上	5%未満	頻度不明
感染症および寄生虫症		結膜炎、口腔ヘルペス、単純ヘルペス	
眼障害		アレルギー性結膜炎、眼瞼炎、眼乾燥	眼そう痒症、角膜炎、潰瘍性角膜炎
血液およびリンパ系障害		好酸球増加症	
注射部位	注射部位紅斑	注射部位反応、注射部位そう痒感、注射部位浮腫	
神経系障害		頭痛	
皮膚および皮下組織障害		発疹	
その他		発熱、関節痛	血清病、血清病様反応

14. 適用上の注意
14.1 薬剤投与前の注意
14.1.1 投与前に300mgシリンジ及び300mgペンは45分以上、200mgシリンジは30分以上かけて室温に戻しておくことが望ましい。
14.1.2 溶液が白濁したり、着色したり、微粒子がみられた場合及びシリンジに損傷がみられた場合には本剤は使用しないこと。
14.1.3 投与直前まで本剤のキャップを外さないこと。キャップを外したら直ちに投与すること。

14.2 薬剤投与時の注意
14.2.1 皮下注射は腹部、大腿部又は上腕部に行うこと。腹部へ投与する場合は、へその周り5cmを外して投与すること。注射部位反応が報告されているので、同一箇所へ繰り返し注射することは避けること。
14.2.2 正常な皮膚の部位に注射すること。皮膚が敏感な部位、皮膚に損傷、打撲や傷のある部位、アトピー性皮膚炎の強い炎症を伴う部位には注射しないこと。
14.2.3 他の薬剤と混合しないこと。
14.2.4 本剤は1回で全量を使用する製剤であり、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
本剤を投与したときの抗薬物抗体（ADA）陽性反応発現割合、持続するADA陽性反応発現割合及び中和抗体陽性反応発現割合について、アトピー性皮膚炎患者では、成人はそれぞれ約6%、約2%及び約1%、12～17歳はそれぞれ約16%、約3%及び約5%、並びに生後6カ月～11歳はそれぞれ約2%、0%及び約1%であった。結節性痒疹患者では、それぞれ約8%、約1%及び約3%、特発性の慢性蕁麻疹患者では、それぞれ約7%、1%及び約2%、気管支喘息患者では、それぞれ約5%、約2%及び約2%、鼻茸を伴う慢性副鼻腔炎患者では、それぞれ約5%、約2%及び約3%であった。なお、プラセボ群のADA陽性反応発現割合、持続するADA陽性反応発現割合及び中和抗体陽性発現割合は、それぞれ約4%、約2%及び約1%であった。高抗体価（10,000超）のADAの発現例（発現頻度1%未満）では、本剤の薬物動態及び有効性への影響が示唆された。加えて、高抗体価のADAに関連した血清病及び血清病様反応が認められた。

16. 薬物動態
16.1 血中濃度
16.1.1 単回投与
日本人健康成人に本剤300mg又は600mgを単回皮下投与したときのデュピルマブの血清中濃度推移及び薬物動態パラメータは以下のとおりであった[1)]。



本剤300mg又は600mgを単回皮下投与したときの血清中濃度推移

本剤300mg又は600mgを単回皮下投与したときの薬物動態パラメータ

投与量（mg）	C_{max}（mg/L）	t_{max}[注1)]（day）	AUC_{last}（mg・day/L）	$t_{1/2z}$[注2)]（day）
300（6例）	38.3±15.3	7.01（6.99-10.00）	700±234	5.13±1.42
600（6例）	70.1±24.1	7.00（3.00-7.02）	1780±699	8.77±5.18

（平均値±標準偏差）
注1）中央値（最小値-最大値）
注2）血清中薬物濃度の経時的推移を片対数プロットしたときの最終消失相の回帰直線の傾きから算出

＊16.1.2 反復投与（成人）
アトピー性皮膚炎、結節性痒疹、特発性の慢性蕁麻疹、気管支喘息及び鼻茸を伴う慢性副鼻腔炎患者（成人）に本剤300mgを隔週で反復投与したときのデュピルマブのトラフ濃度（平均値±標準偏差）を効能別に示す[2, 6, 8, 9)]（日本人及び外国人データ）。

デュピルマブのトラフ濃度

効能	例数（名）	トラフ濃度（mg/L）	週
アトピー性皮膚炎	219	73.3±40.0	16
結節性痒疹	65	60.2±34.7	24
特発性の慢性蕁麻疹	62	63.5±34.2	24
気管支喘息	544	69.0±37.8	24
鼻茸を伴う慢性副鼻腔炎	142	80.2±35.3	24

16.1.3 反復投与（小児）

小児のアトピー性皮膚炎患者に本剤を反復投与したときのデュピルマブのトラフ濃度（平均値±標準偏差）を示す[5]（日本人データ）。

デュピルマブのトラフ濃度

体重	用量	例数（名）	トラフ濃度（mg/L）	週
60kg以上	300mg Q2W	3	90.1±26.2	16
30kg以上60kg未満	200mg Q2W	14	62.5±29.7	16
15kg以上30kg未満	300mg Q4W	7	86.6±29.9	16
5 kg以上15kg未満	200mg Q4W	3	95.7±38.6	16

Q2W：2週に1回投与、Q4W：4週に1回投与

16.1.4 母集団薬物動態解析

本剤は主に血管内のコンパートメントに分布し、母集団薬物動態解析により推定される分布容積は約4.6Lであった。

母集団薬物動態解析により、定常状態時の最終投与から本剤の血清中濃度が定量下限未満に低下する時間の中央値は、300mg隔週投与で10～12週間と推定された。

＊16.2 吸収

母集団薬物動態解析により推定される皮下投与時の絶対バイオアベイラビリティは、アトピー性皮膚炎、結節性痒疹、特発性の慢性蕁麻疹、気管支喘息及び鼻茸を伴う慢性副鼻腔炎患者の間で類似しており、61～64%であった。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈アトピー性皮膚炎〉

17.1.1 国際共同第Ⅲ相併用療法試験（成人）

日本の分類でストロングクラス以上に相当するステロイド外用薬で効果不十分な、18歳以上の中等症から重症[注1)]のアトピー性皮膚炎（AD）患者740例（日本人患者117例を含む）を対象に、ステロイド外用剤に上乗せして本剤300mgを2週に1回（Q2W）又は毎週1回（QW）、若しくはプラセボを52週間投与した。本剤群では投与1日目に初回用量として本剤600mgの投与を行った[注2)]。ベースラインの医師による全般評価（IGA）スコアは3.5±0.5、Eczema Area and Severity Index（EASI）スコアは32.5±12.9であった。主要有効性評価項目とした投与後16週時点のIGA≦1達成率[注3)]及びEASI-75達成率[注4)]において、本剤群はプラセボ群に比べ統計的に有意な（P<0.0001）改善効果を示した[3]。

注1）IGAスコアが3以上、EASIスコアが16以上、及び体表面積に占めるAD病変の割合が10%以上、そう痒NRSスコアの日内最大値の週平均が3点以上

注2）投与期間中は保湿剤の併用を必須とし、経口シクロスポリン、経口ステロイド等の全身療法及び光線療法の併用を禁止した。

注3）IGAスコアが0（消失）又は1（ほぼ消失）かつベースラインから2点以上減少（改善）を達成した患者の割合

注4）EASIスコアがベースラインから75%以上改善した患者の割合

アトピー性皮膚炎・国際共同第Ⅲ相併用療法試験の成績（成人）

全体集団		Q2W群	プラセボ群	プラセボ群との差［95%信頼区間］p値[注5),注6)]
16週	IGA≦1達成率	38.7（41/106）	12.4（39/315）	26.3［16.3, 36.3］<0.0001
	EASI-75達成率	68.9（73/106）	23.2（73/315）	45.7［35.7, 55.7］<0.0001
	そう痒NRS≧4点改善達成率[注7)]	58.8（60/102）	19.7（59/299）	39.1［28.5, 49.7］
52週	IGA≦1達成率	34.9（37/106）	12.4（39/264）	22.5［12.8, 32.3］
	EASI-75達成率	62.3（66/106）	21.9（69/315）	40.4［30.1, 50.7］
	そう痒NRS≧4点改善達成率[注7)]	48.0（49/102）	13.4（40/299）	34.7［24.2, 45.1］
日本人部分集団		Q2W群	プラセボ群	プラセボ群との差［95%信頼区間］
16週	IGA≦1達成率	18.8（3/16）	3.7（2/54）	15.0［−13.2, 41.7］
	EASI-75達成率	62.5（10/16）	22.2（12/54）	40.3［12.5, 65.0］
	そう痒NRS≧4点改善達成率[注7)]	40.0（6/15）	18.9（10/53）	21.1［−7.82, 48.5］
52週	IGA≦1達成率	31.3（5/16）	11.1（6/54）	20.1［−7.78, 46.5］
	EASI-75達成率	50.0（8/16）	24.1（13/54）	25.9［−2.15, 52.3］
	そう痒NRS≧4点改善達成率[注7)]	33.3（5/15）	17.0（9/53）	16.4［−12.5, 44.0］

承認用法・用量である300mg Q2Wのみ提示

%（例数）

中止例又は救済治療例はNon-responderとした。

注5）地域及びベースライン時の重症度（IGAスコア3又は4）を因子として考慮したCochran-Mantel-Haenszel検定（主要有効性評価項目についてのみ表中に表示）

注6）プラセボ群と各本剤群の比較における有意水準をそれぞれ両側2.5%と設定することで、検定の多重性を調整

注7）そう痒NRSスコアの日内最大値の週平均がベースラインから4点以上改善した患者の割合（スコアの最大は10）

本剤Q2W群での副作用は33.6%（37/110例）に、プラセボ群の副作用は28.6%（90/315例）に認められ、主な副作用は本剤Q2W群で注射部位反応10.9%、アレルギー性結膜炎4.5%、眼瞼炎3.6%、アトピー性皮膚炎3.6%、頭痛3.6%であった。［5.1 参照］

17.1.2 国際共同第Ⅲ相単独療法試験（成人）

日本の分類でストロングクラス以上に相当するステロイド外用薬で効果不十分な、又は安全性上の理由等[注1)]からステロイド外用薬が推奨されない、18歳以上の中等症から重症[注2)]のAD患者671例（日本人患者106例を含む）を対象に、本剤300mgをQ2W又はQW、若しくはプラセボを16週間投与した[注3)]。本剤群では投与1日目に初回用量として本剤600mgの投与を行った。ベースラインのIGAスコアは3.5±0.5、EASIスコアは33.6±14.0であった。主要有効性評価項目とした投与後16週時点のIGA≦1達成率[注4)]及びEASI-75達成率[注5)]において、本剤群はプラセボ群に比べ統計的に有意な（P<0.0001）改善効果を示した[4]。

注1）ステロイド外用薬治療により副作用（治療不耐容、過敏症反応、顕著な皮膚萎縮、全身性の影響など）を認めた患者

注2）IGAスコアが3以上、EASIスコアが16以上、及び体表面積に占めるAD病変の割合が10%以上、そう痒NRSスコアの日内最大値の週平均が3点以上

注3）投与期間中は保湿剤の併用を必須とし、経口シクロスポリン、経口ステロイド等の全身療法及び光線療法の併用を禁止した。

注4）IGAスコアが0（消失）又は1（ほぼ消失）かつベースラインから2点以上減少（改善）を達成した患者の割合

注5）EASIスコアがベースラインから75%以上改善した患者の割合

アトピー性皮膚炎・国際共同第Ⅲ相単独療法試験の成績（成人）

全体集団	Q2W群	プラセボ群	プラセボ群との差［95%信頼区間］p値[注6),注7)]
IGA≦1達成率	37.9（85/224）	10.3（23/224）	27.7［20.2, 35.2］<0.0001
EASI-75達成率	51.3（115/224）	14.7（33/224）	36.6［28.6, 44.6］<0.0001
そう痒NRS≧4点改善達成率[注8)]	40.8（87/213）	12.3（26/212）	28.6［20.7, 36.5］
日本人部分集団	Q2W群	プラセボ群	プラセボ群との差［95%信頼区間］
IGA≦1達成率	19.4（7/36）	2.9（1/35）	16.6［-6.36, 38.8］
EASI-75達成率	25.0（9/36）	0.0（0/35）	25.0［2.16, 46.5］
そう痒NRS≧4点改善達成率[注8)]	25.0（8/32）	0.0（0/34）	25.0［1.35, 47.6］

承認用法・用量である300mg Q2Wのみ提示
%（例数）
中止例又は救済治療例はNon-responderとした。
注6）地域及びベースライン時の重症度（IGAスコア3又は4）を因子として考慮したCochran-Mantel-Haenszel検定（主要有効性評価項目についてのみ）
注7）プラセボ群と各本剤群の比較における有意水準をそれぞれ両側2.5%と設定することで、検定の多重性を調整
注8）そう痒NRSスコアの日内最大値の週平均がベースラインから4点以上改善した患者の割合（スコアの最大は10）

本剤Q2W群での副作用は28.8%（66/229例）に、プラセボ群に18.0%（40/222例）に認められ、主な副作用は本剤Q2W群に注射部位反応7.4%、アトピー性皮膚炎3.5%、頭痛3.1%であった。［5.1 参照］

17.1.3 国内第Ⅲ相試験（生後6カ月以上18歳未満の小児）

日本の分類でミディアムからストロングクラスのステロイド外用薬で効果不十分な、生後6カ月以上18歳未満の中等症から重症[注1)]の日本人AD患者62例を対象に、ステロイド外用剤に上乗せしてベースライン時の体重に応じて以下の用法・用量で本剤又はプラセボを16週間、盲検下で投与した[注2)]。

・体重5kg以上15kg未満：1回200mgを4週に1回（Q4W）
・体重15kg以上30kg未満：1回300mgをQ4W
・体重30kg以上60kg未満：投与1日目に初回用量400mg、その後200mgをQ2W
・体重60kg以上：投与1日目に初回用量600mg、その後300mgをQ2W

ベースライン時のEASIスコアは25.2±6.8であった。主要有効性評価項目とした投与後16週時点のEASI-75達成率[注3)]において、本剤群はプラセボ群に比べ統計的に有意な（P値：0.0304）改善効果を示した[5)]。

注1）IGAスコアが3以上、EASIスコアが16以上、体表面積に占めるAD病変の割合が10%超、そう痒NRSスコアの日内最大値の週平均が4点以上（12歳以上18歳未満）、痒みNRSスコアの日内最悪値の週平均が4点以上（6歳以上12歳未満）、又は掻破／痒みNRSスコアの日内最悪値の週平均が4点以上（生後6カ月以上6歳未満）
注2）投与期間中は保湿剤の併用を必須とし、経口シクロスポリン、経口ステロイド等の全身療法及び光線療法の併用を禁止した。
注3）EASIスコアがベースラインから75%以上改善した患者の割合

アトピー性皮膚炎・国内第Ⅲ相併用療法試験の成績（小児）

日本人集団	本剤群	プラセボ群	プラセボ群との差［95%信頼区間］p値[注4)]
EASI-75達成率	43.3（13/30）	18.8（6/32）	25.1［3.26, 46.90］0.0304

%（例数）
注4）層別因子（ベースライン時で生後6カ月以上6歳未満、6歳以上12歳未満かつIGAスコアが3、6歳以上12歳未満かつIGAスコアが4、12歳以上）を因子として考慮したCochran-Mantel-Haenszel検定

また、投与後52週時点（非盲検延長期）における本剤群のEASI-75達成率は62.9%であった。

投与16週までの本剤群での副作用は16.7%（5/30例）、プラセボ群では9.4%（3/32例）に認められ、本剤群の主な副作用はアレルギー性結膜炎6.7%であった。［5.1 参照］

〈結節性痒疹〉

17.1.4 国際共同第Ⅲ相試験

日本の分類でウィークからベリーストロングのステロイド外用薬で効果不十分[注1)]な、又はステロイド外用薬が推奨されない、18歳以上の結節性痒疹[注2)]患者151例（日本人患者16例を含む）を対象に、本剤300mgを2週に1回（Q2W）、又はプラセボを24週間投与した。本剤群では投与1日目に初回用量として本剤600mgの投与を行った。主要評価項目である投与後24週時点のWI-NRSスコア[注3)]がベースラインから4点以上改善した患者の割合において、本剤群はプラセボ群に比べ統計的に有意な（P<0.0001）改善を示した[6)]。

注1）ステロイド外用薬を2週間使用しても最悪のそう痒スコア（WI-NRSスコア）が週平均で7以上、両脚、両腕又は体幹の少なくとも2つの体表面領域に合計20か所以上の結節性痒疹の病変（IGA PN-Sスコアが3又は4相当）を有する患者
注2）次の所見に基づき診断；6週間以上の持続する慢性そう痒がある、繰り返し掻く病歴又は徴候がある、多発性の限局性／全身性痒疹の結節性皮膚病変がある

投与後24週時点の有効性の成績（ITT集団）

評価項目	本剤群	プラセボ群	プラセボ群との差［95%信頼区間］p値[注4)]
WI-NRS≧4点改善達成率[注3)]	60.0（45/75）	18.4（14/76）	42.7（27.76, 57.72）<0.0001
IGA PN-S（0又は1）達成率[注3)]	48.0（36/75）	18.4（14/76）	28.3（13.41, 43.16）

注3）WI-NRSスコア（0-10点のスケールで評価される過去24時間の最悪のそう痒の程度の週平均）；IGA PN-Sスコア（0-4点のスケールで評価される結節性痒疹の病期に関する医師による全般評価）
WI-NRSスコア、IGA PN-Sスコアはスコアの減少が改善を意味する。
注4）アトピーの既往の有無、外用ステロイド薬又は外用カルシニューリン阻害薬の使用の有無、地域及びベースライン時の抗うつ薬使用の有無を因子として考慮したCochran-Mantel-Haenszel検定（主要有効性評価項目についてのみ表示）

本剤群での副作用は14.7%（11/75例）、プラセボ群では13.3%（10/75例）に認められ、本剤群の主な副作用は注射部位反応4.0%であった。［5.4 参照］

〈特発性の慢性蕁麻疹〉

＊17.1.5 国際共同第Ⅲ相試験

第二世代ヒスタミンH_1受容体拮抗薬の使用で効果不十分[注1)]な6歳以上の特発性の慢性蕁麻疹患者138例（12歳以上の小児患者4名及び6歳以上12歳未満の小児患者2名[注2)]を含む、そのうち12名の日本人［いずれも成人］を含む）を対象に、本剤300mgを2週に1回（成人及び60kg以上の12歳以上の小児患者）又は本剤200mgを2週に1回（60kg未満の12歳以上の小児患者及び30kg以上の6歳以上12歳未満の小児患者）、又はプラセボを24週間投与した。本剤群では投与1日目に初回用量として本剤600mg（300mgを2週に1回の場合）又は400mg

（200mgを２週に１回の場合）の投与を行った。主要評価項目である投与24週時における７日間のそう痒重症度スコア（ISS7）のベースラインからの変化量（減少）において、本剤群はプラセボ群に比べ統計的に有意な（P=0.0005）改善効果を示した[7]。

注1）ランダム化前のUAS7及びISS7がそれぞれ16及び８以上を有するオマリズマブの投与歴のない患者

注2）６歳以上12歳未満の小児患者はいずれも治験薬投与を早期に中止した

投与24週後のISS7[注3]の変化量（ITT集団）

全体集団	本剤群	プラセボ群
ベースライン	16.10±3.98（70）	15.74±4.11（68）
投与24週後[注4]	5.28±5.88（64）	8.06±6.64（53）
ベースラインからの変化量	−10.24 ［−12.03, −8.46］	−6.01 ［−7.85, −4.17］
プラセボ群との差[注5] ［95%信頼区間］ p値	−4.23 ［−6.63, −1.84］ 0.0005	

平均値±標準偏差（例数）又は最小二乗平均値［95%CI］

注3）０-３点のスケールで評価される過去24時間のそう痒の程度を毎日同じ時間に記録して７日間合計したそう痒重症度スコア（範囲は０～21）

注4）救済治療を受けた患者を含む実測値

注5）補完された完全データの各々についてベースライン値、投与群、ベースライン時の血管性浮腫の有無、および地域を共変量とした共分散分析により解析を行った。

本剤投与群での副作用は14.3%（10/70例）、プラセボ群では23.5%（16/68例）に認められ、本剤群の主な副作用は注射部位紅斑4.3%、及び注射部位反応4.3%であった。［5. 6、7. 3 参照］

〈気管支喘息〉

17. 1. 6 国際共同第Ⅲ相試験

中用量又は高用量の吸入ステロイド薬及び他の長期管理薬で治療しても喘息増悪をきたす12歳以上の気管支喘息患者1902例[注1]（日本人患者114例を含む）を対象に、既存治療の併用下で、本剤200mg[注2]又は300mg[注2]、もしくはそれぞれと対応するプラセボを52週間Q2W投与した。主要有効性評価項目とした喘息増悪（全身ステロイド薬による３日間以上の治療、又は全身ステロイド薬による治療が必要な喘息による入院若しくは救急外来の受診）の発生率[注3]及び12週時点のFEV_1の変化量[注4]で、本剤300mg群はプラセボ群と比べて統計的に有意な効果を示した[8]。

注1）ベースライン時の血中好酸球数が1,500/μL超の患者は除外した。

注2）投与開始時には初回用量としてそれぞれ400mg又は600mgを投与

注3）52週間の治験薬投与期間中における重度喘息増悪の年換算発生率

注4）投与開始後12週時点における気管支拡張薬投与前のFEV_1のベースラインからの変化量

投与52週後までの年間重度喘息増悪発生率（ITT集団）

全体集団	300mg群 （633例）	プラセボ群 （321例）
総観察期間（人・年）	612.5	313.2
喘息増悪発生件数(回)	343	342
年間増悪発生率 （回/人・年）	0.560	1.092
年間増悪発生率[注5] （回/人・年） ［95%信頼区間］	0.524 ［0.450, 0.611］	0.970 ［0.810, 1.160］
プラセボ群との比[注5] ［95%信頼区間］ p値[注5]	0.540 ［0.430, 0.680］ <0.0001	

日本人部分集団	300mg群 （41例）	プラセボ群 （17例）
総観察期間（人・年）	40.2	17.0
喘息増悪発生件数(回)	17	21
年間増悪発生率 （回/人・年）	0.423	1.238
年間増悪発生率[注5] （回/人・年） ［95%信頼区間］	0.309 ［0.139, 0.687］	1.232 ［0.502, 3.025］
プラセボ群との比[注5] ［95%信頼区間］	0.251 ［0.072, 0.874］	

注5）投与群、年齢、地域、ベースライン時の血中好酸球数区分、ベースライン時のICS用量、１年以内の重度喘息増悪の発生回数を説明変数とし、観察期間の対数変換値をオフセット変数とした負の二項回帰モデル

投与12週後の気管支拡張薬投与前FEV_1（L）の変化量（ITT集団）

全体集団	300mg群	プラセボ群
ベースライン	1.78±0.60（633）	1.75±0.57（321）
投与12週後	2.09±0.70（610）	1.93±0.68（313）
ベースラインからの変化量	0.31±0.43（610）	0.18±0.39（313）
プラセボ群との差[注6] ［95%信頼区間］ p値[注6]	0.13 ［0.08, 0.18］ <0.0001	
日本人部分集団	300mg群	プラセボ群
ベースライン	1.75±0.64（41）	1.76±0.43（17）
投与12週後	2.02±0.63（41）	1.88±0.55（17）
ベースラインからの変化量	0.28±0.43（41）	0.12±0.32（17）
プラセボ群との差[注6] ［95%信頼区間］	0.17 ［−0.04, 0.37］	

平均値±標準偏差（例数）

注6）投与群、年齢、性別、身長、地域、ベースライン時の血中好酸球数区分、ベースライン時のICS用量、評価時点、投与群と評価時点の交互作用、ベースライン値、ベースライン値と評価時点の交互作用を説明変数としたMMRM法、相関構造にはunstructuredを仮定した。

バイオマーカーの区分別の投与52週後までの年間重度喘息増悪発生率（ITT集団）

マーカー	区分 （ベースライン時）	重度喘息増悪の年間発生率		プラセボ群との比[注7] ［95%信頼区間］
		300mg群	プラセボ群	
血中好酸球数	150/μL未満	0.805（181）	0.779（83）	1.149 ［0.747, 1.767］
	150/μL以上 300/μL未満	0.475（175）	0.845（95）	0.557 ［0.350, 0.888］
	300/μL以上 500/μL未満	0.496（136）	1.393（68）	0.366 ［0.225, 0.596］
	500/μL以上	0.413（141）	1.486（74）	0.287 ［0.184, 0.449］
FeNO	25ppb未満	0.639（317）	0.863（144）	0.792 ［0.572, 1.098］
	25ppb以上 50ppb未満	0.489（186）	1.183（97）	0.442 ［0.282, 0.693］
	50ppb以上	0.485（124）	1.444（75）	0.305 ［0.188, 0.494］
総IgE濃度	61IU/mL未満	0.681（149）	0.792（83）	0.817 ［0.511, 1.307］
	61IU/mL以上 167IU/mL未満	0.535（156）	1.344（74）	0.420 ［0.275, 0.641］
	167IU/mL以上 449IU/mL未満	0.616（164）	1.008（84）	0.685 ［0.424, 1.106］
	449IU/mL以上	0.402（157）	1.291（77）	0.375 ［0.232, 0.606］

回/人・年（例数）

注7）投与群、年齢、地域、ベースライン時の血中好酸球数区分、ベースライン時のICS用量、１年以内の重度喘息増悪の発生回数を説明変数とし、観察期間の対数変換値をオフセット変数とした負の二項回帰モデル

バイオマーカーの区分別の投与12週後の気管支拡張薬投与前FEV_1（L）の変化量（ITT集団）

マーカー	区分（ベースライン時）	ベースラインからの変化量		プラセボ群との差[注8] ［95%信頼区間］
		300mg群	プラセボ群	
血中好酸球数	150/μL未満	0.19±0.37（176）	0.11±0.41（83）	0.09［−0.01, 0.18］
	150/μL以上 300/μL未満	0.22±0.45（168）	0.22±0.36（90）	−0.00［−0.10, 0.10］
	300/μL以上 500/μL未満	0.36±0.39（131）	0.17±0.39（66）	0.18［0.07, 0.30］
	500/μL以上	0.50±0.45（135）	0.22±0.41（73）	0.30［0.19, 0.42］
FeNO	25ppb未満	0.20±0.37（309）	0.17±0.36（141）	0.03［−0.04, 0.10］
	25ppb以上 50ppb未満	0.32±0.40（182）	0.18±0.37（94）	0.12［0.03, 0.21］
	50ppb以上	0.59±0.51（113）	0.20±0.48（73）	0.39［0.26, 0.52］
総IgE濃度	61IU/mL未満	0.21±0.36（143）	0.19±0.39（78）	0.05［−0.04, 0.14］
	61IU/mL以上 167IU/mL未満	0.28±0.38（151）	0.23±0.40（73）	0.05［−0.05, 0.15］
	167IU/mL以上 449IU/mL未満	0.34±0.47（156）	0.08±0.31（83）	0.26［0.15, 0.36］
	449IU/mL以上	0.39±0.49（154）	0.24±0.46（76）	0.13［0.01, 0.25］

平均値±標準偏差（例数）

注8）投与群、年齢、性別、身長、地域、ベースライン時の血中好酸球数区分、ベースライン時のICS用量、評価時点、投与群と評価時点の交互作用、ベースライン時のFEV_1値、ベースラインと評価時点の交互作用を説明変数としたMMRM法、相関構造にはunstructuredを仮定した。

本剤300mg群での副作用は22.6%（143/632例）に、プラセボ群では14.0%（45/321例）に認められ、主な副作用は本剤300mgに注射部位紅斑14.9%、注射部位浮腫5.9%、注射部位そう痒症4.7%であった。［5.8 参照］

〈鼻茸を伴う慢性副鼻腔炎〉

17.1.7 国際共同第Ⅲ相試験

手術や全身ステロイド薬（推奨されない場合を除く）によっても効果不十分[注1)]な、18歳以上の鼻茸を伴う慢性副鼻腔炎患者448例（日本人患者49例を含む）を対象に、鼻噴霧用ステロイド薬に追加して本剤300mgを52週間2週に1回（Q2W）（Q2W群）又は最初の24週間はQ2Wその後52週まで4週に1回（Q4W）投与（Q2W-Q4W群）、若しくはプラセボを52週間投与した。3つの主要有効性評価項目である投与後24週時点の鼻茸スコア、鼻閉重症度スコア、Lund-Mackay（LMK）スコアのベースラインからの変化量において、本剤併合群（Q2W群及びQ2W-Q4W群）はプラセボ群に比べ統計的に有意な改善を示した（全てp<0.0001）[9)]。

注1）両側鼻茸スコアが5以上（各鼻孔スコアは2以上）、鼻閉重症度スコアが2以上で週平均が1を超える、嗅覚障害や鼻漏（前鼻漏／後鼻漏）といったその他の症状を有する患者

ベースラインからの変化量の調整平均及び群間差（ITT集団）

評価項目			本剤併合群[注6]（295例）	プラセボ群（153例）
投与後24週時点	鼻茸スコア[注2]	投与前[注3]	6.18	5.96
		変化量[注4]	−1.71	0.10
		プラセボ群との差［95%信頼区間］[注5]	−1.80［−2.10, −1.51］	
	鼻閉重症度[注2]	投与前[注3]	2.46	2.38
		変化量[注4]	−1.25	−0.38
		プラセボ群との差［95%信頼区間］[注5]	−0.87［−1.03, −0.71］	
	LMKスコア[注2]	投与前[注3]	18.12	17.65
		変化量[注4]	−5.21	−0.09
		プラセボ群との差［95%信頼区間］[注5]	−5.13［−5.80, −4.46］	
	UPSIT[注2]	投与前[注3]	13.53	13.78
		変化量[注4]	9.71	−0.81
		プラセボ群との差［95%信頼区間］[注5]	10.52［8.98, 12.07］	

評価項目			本剤Q2W群（150例）	本剤Q2W-Q4W群（145例）	プラセボ群（153例）
投与後52週時点	鼻茸スコア[注2]	投与前[注3]	6.07	6.29	5.96
		変化量[注4]	−2.24	−2.06	0.15
		プラセボ群との差［95%信頼区間］[注5]	−2.40［−2.77, −2.02］	−2.21［−2.59, −1.83］	
	鼻閉重症度[注2]	投与前[注3]	2.48	2.44	2.38
		変化量[注4]	−1.35	−1.48	−0.37
		プラセボ群との差［95%信頼区間］[注5]	−0.98［−1.17, −0.79］	−1.10［−1.29, −0.91］	
	LMKスコア[注2]	投与前[注3]	18.42	17.81	17.65
		変化量[注4]	−6.83	−5.60	0.11
		プラセボ群との差［95%信頼区間］[注5]	−6.94［−7.87, −6.01］	−5.71［−6.64, −4.77］	
	UPSIT[注2]	投与前[注3]	13.46	13.60	13.78
		変化量[注4]	9.53	9.99	−0.77
		プラセボ群との差［95%信頼区間］[注5]	10.30［8.50, 12.10］	10.76［8.95, 12.57］	

注2）鼻茸スコア（0－8点）; 鼻閉重症度（0－3点）; LMK（sinus opacification on the Lund-MacKay total CT）スコア（0－24点）; UPSIT（University of Pennsylvania smell identification test）（0－40点）
鼻茸スコア、鼻閉重症度スコア、LMKスコアはスコアの減少が、UPSITはスコアの増加が改善を意味する。

注3）平均値

注4）調整平均

注5）WOCF法及び多重代入法を合わせた混成手法により、投与群、喘息の状態、手術歴及び地域を要因とし、ベースライン値を共変量とした共分散分析で解析した。

注6）Q2W群とQ2W-Q4W群の併合

本剤Q2W群での副作用は24.2%（36/149例）、Q2W-Q4W群では27.7%（41/148例）、プラセボ群では22.0%（33/150例）に認められ、本剤Q2W群及びQ2W-Q4W群の主な副作用は注射部位紅斑7.4%及び6.8%、及び注射部位反応3.4%及び5.4%であった。

18. 薬効薬理

＊18.1 作用機序

デュピルマブは、ヒトインターロイキン-4及びインターロイキン-13受容体の複合体が共有しているIL-4受容体αサブユニットに特異的に結合することにより、IL-4及びIL-13の両シグナル伝達を阻害する遺伝子組換えヒトIgG4モノクローナル抗体である。IL-4及びIL-13はアトピー性皮膚炎、結節性痒疹、特

発性の慢性蕁麻疹、気管支喘息及び鼻茸を伴う慢性副鼻腔炎の病態において重要な役割を担うType 2サイトカインである[10]。

18.2 IL-4及びIL-13シグナル伝達に対する作用

デュピルマブは高親和性にヒトIL-4Rαに結合し、IL-4及びIL-13を介したシグナル伝達を*in vitro*及び*in vivo*で抑制した[10]。

18.3 2型炎症モデルにおける炎症抑制作用

内因性マウスIL-4及びIL-4Rαの外部領域の両方を、相当するヒト配列で置換した遺伝子改変マウスを用いたチリダニアレルゲン誘発性Type 2炎症モデルにおいて、デュピルマブは、血清中IgE濃度、アレルゲン特異的IgG1濃度等を低下させるとともに、肺好酸球浸潤、杯細胞化生並びに肺機能障害を抑制した[10]。

19. 有効成分に関する理化学的知見

一般的名称：デュピルマブ（遺伝子組換え）
Dupilumab（Genetical Recombination）

本　　質：デュピルマブは、ヒトインターロイキン-4受容体のαサブユニットに対する遺伝子組換えヒトIgG4モノクローナル抗体であり、H鎖233番目のアミノ酸残基がProに置換されている。デュピルマブは、チャイニーズハムスター卵巣細胞により産生される。デュピルマブは、452個のアミノ酸残基からなるH鎖（γ4鎖）2本及び219個のアミノ酸残基からなるL鎖（κ鎖）2本で構成される糖タンパク質（分子量：約152,000）である。

20. 取扱い上の注意

20.1 外箱開封後は遮光して保存すること。

20.2 本剤を温めたり、直射日光に晒さないこと。また、本剤を振とうしないこと。

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 鼻噴霧用ステロイド薬非併用下における本剤の有効性及び安全性を確認するための臨床試験を製造販売後に実施すること。

22. 包装

〈デュピクセント皮下注300mgペン〉
2mL×1本

〈デュピクセント皮下注300mgシリンジ〉
2mL×1本

〈デュピクセント皮下注200mgシリンジ〉
1.14mL×1本

＊23. 主要文献

1）社内資料：国内第Ⅰ相単回投与試験（2018年1月19日承認、CTD2.7.2.2）
2）社内資料：アトピー性皮膚炎患者を対象とした国際共同第Ⅲ相単独療法試験（2018年1月19日承認、CTD2.7.2.2）
3）社内資料：アトピー性皮膚炎患者を対象とした国際共同第Ⅲ相併用療法試験（2018年1月19日承認、審査報告書p.33-34）
4）Simpson E L, et al.：N Engl J Med. 2016;375(24):2335-48
5）社内資料：生後6カ月以上18歳未満のアトピー性皮膚炎患者を対象とした国内第Ⅲ相併用療法試験（2023年9月25日承認、審査報告書p.8-11）
6）社内資料：結節性痒疹患者を対象とした国際共同第Ⅲ相試験（2023年6月26日承認、審査報告書p.8-9）
7）社内資料：特発性の慢性蕁麻疹患者を対象とした国際共同第Ⅲ相試験（2024年2月9日承認、審査報告書p.7-9）
8）社内資料：気管支喘息患者を対象とした国際共同第Ⅲ相試験（2019年3月26日承認、審査報告書p.15）
9）Bachert C, et al.：Lancet. 2019;394(10209):1638-50
10）社内資料：非臨床薬効薬理試験（2018年1月19日承認、CTD2.6.2.1）

24. 文献請求先及び問い合わせ先

サノフィ株式会社
くすり相談室
〒163-1488　東京都新宿区西新宿三丁目20番2号
フリーダイヤル 0120-109-905

26. 製造販売業者等

26.1 製造販売元

サノフィ株式会社
〒163-1488　東京都新宿区西新宿三丁目20番2号

26.2 販売提携

リジェネロン・ジャパン株式会社

1.8. 添付文書（案）

＊添付文書（案）は審査段階のものであり、
最新の添付文書を参照すること。

＊新薬承認情報提供時に記載

20xx年x月改訂（第x版、効能変更）（____：本申請に伴う変更箇所）

日本標準商品分類番号
87229

ヒト化抗 IL-5 モノクローナル抗体

メポリズマブ（遺伝子組換え）製剤

貯法：2～8℃で保存
有効期間：36ヵ月

規制区分：
生物由来製品、
劇薬、
処方箋医薬品[注)]
注)注意－医師等の処方箋により使用すること

ヌーカラ皮下注 100mg ペン
ヌーカラ皮下注 100mg シリンジ
小児用ヌーカラ皮下注 40mg シリンジ

NUCALA solution for s.c. injection

NUCALA solution for s.c. injection for Pediatric

（一部）最適使用推進ガイドライン対象品目

	100mg ペン	100mg シリンジ	小児用 40mg シリンジ
承認番号	30200AMX00451	30200AMX00450	30400AMX00204
販売開始	2020 年 5 月		2022 年 11 月

2. 禁忌（次の患者には投与しないこと）
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	ヌーカラ 皮下注 100mg ペン	ヌーカラ 皮下注 100mg シリンジ	小児用ヌーカラ 皮下注 40mg シリンジ
有効成分	1 ペン又は 1 シリンジ（1mL）中 メポリズマブ（遺伝子組換え） 100mg		1 シリンジ（0.4mL）中 メポリズマブ（遺伝子組換え） 40mg
添加剤	精製白糖 120.0mg リン酸水素二ナトリウム七水和物 4.16mg クエン酸水和物 0.95mg ポリソルベート 80 0.20mg エデト酸ナトリウム水和物 0.019mg		精製白糖 48.0mg リン酸水素二ナトリウム七水和物 1.66mg クエン酸水和物 0.38mg ポリソルベート 80 0.08mg エデト酸ナトリウム水和物 0.0074mg

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。メポリズマブ（遺伝子組換え）のセルバンクの培養に使用する培地成分の製造において、ブタ由来成分（カルボキシペプチダーゼ B）及びウシの膵臓由来成分（トリプシン）を使用している。

3.2 製剤の性状

販売名	ヌーカラ 皮下注 100mg ペン	ヌーカラ 皮下注 100mg シリンジ	小児用ヌーカラ 皮下注 40mg シリンジ
剤形・性状	無色～微黄色又は微褐色の液		
pH	6.0～6.6		
浸透圧	415～615mOsm/kg		

4. 効能又は効果
100mg ペン、100mg シリンジ
○気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）
○既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症
○鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）[注)]
小児用 40mg シリンジ
気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）
注）最適使用推進ガイドライン対象

5. 効能又は効果に関連する注意
〈気管支喘息〉
5.1 高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。
5.2 投与前の血中好酸球数が多いほど本剤の気管支喘息増悪発現に対する抑制効果が大きい傾向が認められている。また、データは限られているが、投与前の血中好酸球数が少ない患者では、十分な気管支喘息増悪抑制効果が得られない可能性がある。本剤の作用機序及び臨床試験で認められた投与前の血中好酸球数と有効性の関係を十分に理解し、患者の血中好酸球数を考慮した上で、適応患者の選択を行うこと。[17.1.1、17.1.2 参照]
5.3 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。
〈好酸球性多発血管炎性肉芽腫症〉
5.4 過去の治療において、全身性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、本剤を上乗せして投与を開始すること。
〈鼻茸を伴う慢性副鼻腔炎〉
5.5 本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。[17.1.4 参照]

6. 用法及び用量
100mg ペン、100mg シリンジ
〈気管支喘息〉
通常、成人及び 12 歳以上の小児にはメポリズマブ（遺伝子組換え）として 1 回 100mg を 4 週間ごとに皮下に注射する。
〈好酸球性多発血管炎性肉芽腫症〉
通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 300mg を 4 週間ごとに皮下に注射する。
〈鼻茸を伴う慢性副鼻腔炎〉
通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 100mg を 4 週間ごとに皮下に注射する。
小児用 40mg シリンジ
〈気管支喘息〉
通常、6 歳以上 12 歳未満の小児にはメポリズマブ（遺伝子組換え）として 1 回 40mg を 4 週間ごとに皮下に注射する。

7. 用法及び用量に関連する注意
〈好酸球性多発血管炎性肉芽腫症〉
7.1 本剤とシクロホスファミドを併用投与した場合の安全性は確認されていない。[17.1.3 参照]
〈鼻茸を伴う慢性副鼻腔炎〉
7.2 本剤による治療反応は、通常投与開始から 24 週までには得られる。24 週までに治療反応が得られない場合は、漫然と投与を続けないよう注意すること。

8. 重要な基本的注意

8.1 本剤の投与は、適応疾患の治療に精通している医師のもとで行うこと。

8.2 本剤はヒトインターロイキン-5（IL-5）と結合し、IL-5 の機能を阻害することにより血中好酸球数を減少させる。好酸球は一部の寄生虫（蠕虫）感染に対する免疫応答に関与している可能性がある。患者が本剤投与中に蠕虫類に感染し、抗蠕虫薬による治療が無効な場合には、本剤投与の一時中止を考慮すること。[9.1.1 参照]

8.3 長期ステロイド療法を受けている患者において、本剤投与開始後にステロイド薬を急に中止しないこと。ステロイド薬の減量が必要な場合には、医師の管理下で徐々に行うこと。

8.4 本剤の投与期間中に喘息に関連した事象及び喘息の悪化が現れることがある。本剤の投与開始後に喘息症状がコントロール不良であったり、悪化した場合には、医師の診察を受けるよう患者に指導すること。

8.5 本剤の投与によって合併する他の好酸球関連疾患の症状が変化する可能性があり、当該好酸球関連疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤の投与中止後の疾患管理も含めて、本剤投与中から、合併する好酸球関連疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。

8.6 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督の下で投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者又はその保護者が理解し、患者又はその保護者自ら確実に投与できることを確認した上で、医師の管理指導の下で実施すること。自己投与の適用後、本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止し医療施設に連絡するよう患者又はその保護者に指導し、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、使用済みの注射器を再使用しないように患者又はその保護者に注意を促し、安全な廃棄方法について指導すること。

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 蠕虫類に感染している患者

本剤投与開始前に蠕虫感染を治療すること。[8.2 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。サルではメポリズマブが胎盤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。サルではメポリズマブが乳汁中へわずかに移行することが報告されている。

9.7 小児等

〈気管支喘息〉

9.7.1 6 歳未満の小児等を対象とした臨床試験は実施していない。

〈好酸球性多発血管炎性肉芽腫症、鼻茸を伴う慢性副鼻腔炎〉

9.7.2 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

一般に、生理機能が低下している。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

アナフィラキシー（頻度不明）

11.2 その他の副作用

	5%以上	1%以上 5%未満	1%未満
過敏症		過敏症反応（蕁麻疹、血管性浮腫、発疹、気管支痙攣、低血圧）	
感染症			下気道感染症、咽頭炎、尿路感染
精神神経系	頭痛		
呼吸器			鼻閉
胃腸障害			上腹部痛
皮膚			湿疹
筋骨格系			背部痛
全身障害			発熱
投与部位	注射部位反応（疼痛、紅斑、腫脹、そう痒、灼熱感）		

14. 適用上の注意

14.1 薬剤交付時の注意

患者又はその保護者には本剤に添付の使用説明書を渡し、使用方法を指導すること。

14.2 薬剤投与前の注意

14.2.1 投与前に室温で最低 30 分放置する。

14.2.2 開封後、8 時間以内に投与する。8 時間以内に投与しなかった場合は廃棄すること。

14.3 薬剤投与時の注意

〈効能共通〉

14.3.1 注射部位は上腕部、大腿部又は腹部とすること。

14.3.2 本剤は 1 回使用の製剤であり、1 回に全量を使用し再使用しないこと。使用後は針が格納されるため、分解しないこと。

〈好酸球性多発血管炎性肉芽腫症〉

14.3.3 100mg ずつ 3 ヵ所に分けて投与し、各注射部位は 5cm 以上離すこと。

16. 薬物動態

16.1 血中濃度

16.1.1 健康成人

健康成人にヌーカラ皮下注 100mg シリンジ及びヌーカラ皮下注 100mg ペンをそれぞれ単回皮下投与した時の血漿中メポリズマブ濃度推移を図 1 に、薬物動態パラメータを表 1 に示す（外国人データ）。

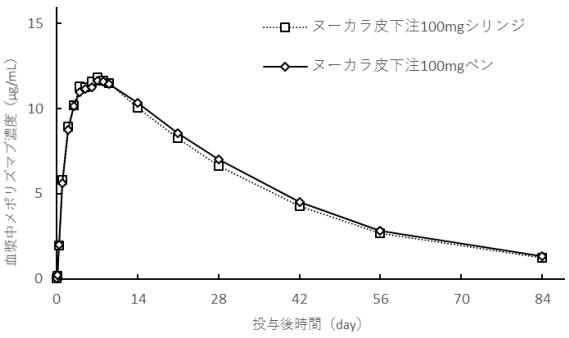


図 1 健康成人にメポリズマブ 100mg を単回皮下投与した時の血漿中メポリズマブ濃度推移（平均値）

表 1 健康成人にメポリズマブ 100mg を単回皮下投与した時の薬物動態パラメータ

薬物動態パラメータ	ヌーカラ皮下注 100mg シリンジ (80 例)	ヌーカラ皮下注 100mg ペン (79 例)
AUC_{0-t}（μg・day/mL）	432.45（117.841）	446.76（101.053）
Cmax（μg/mL）	12.55（3.427）	12.40（3.094）
tmax 注1)（日）	7.06（1.9-14.0）	7.05（2.9-21.0）

$t_{1/2}$（日）	22.40（4.843）	22.90（4.896）

平均値（SD）
注 1）中央値（範囲）

16.1.2 重症喘息患者

(1) 成人及び 12 歳以上の小児

重症喘息患者にメポリズマブ 100mg を 4 週間ごとに皮下投与した時の定常状態における薬物動態パラメータの母集団薬物動態解析に基づく推定値を表 2 に示す。

表 2 重症喘息患者にメポリズマブ 100mg を皮下投与した時の定常状態における薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

薬物動態パラメータ	日本人（16 例）	外国人（175 例）
Cmax ss（ng/mL）	20048.5 (5513.72)	17162.3 (5014.53)
AUC ss（μg･day/mL）	405.9（145.78）	359.1（121.66）

平均値（SD）

(2) 6 歳以上 12 歳未満の小児

6～11 歳の小児重症喘息患者にメポリズマブ 40mg 又は 100mg [注)] を 4 週間ごとに皮下投与した時の薬物動態パラメータの母集団薬物動態解析に基づく推定値を表 3 に示す。

表 3 6～11 歳の小児重症喘息患者にメポリズマブ 40mg 又は 100mg を皮下投与した時の薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

用法・用量[注1)]	薬物動態パラメータ	日本人	外国人
40mg	Cmax[注2)]（μg/mL）	16.50（2.39） (6例)	18.20（2.25） (17例)
	AUC ss（μg･day/mL）	411.92 (72.94) (6例)	478.03（80.99） (20例)
100mg	Cmax[注2)]（μg/mL）	30.50 (1例)	27.06（4.08） (9例)
	AUC ss（μg･day/mL）	748.87 (1例)	675.78 (140.53) (9例)

平均値（SD）
注 1）体重が 40kg 未満の患者に対してはメポリズマブ 40mg を、40kg 以上の患者に対してはメポリズマブ 100mg を 4 週間ごとに投与した。なお、本剤の承認用量は 6 歳以上 12 歳未満の小児気管支喘息では 40mg である。
注 2）メポリズマブ 40mg 又は 100mg を 4 週間ごとに 3 回皮下投与した後の Cmax

16.1.3 好酸球性多発血管炎性肉芽腫症患者

好酸球性多発血管炎性肉芽腫症患者にメポリズマブ 300mg を 4 週間ごとに皮下投与した時の定常状態における血漿中メポリズマブ濃度を表 4 に示す。

表 4 好酸球性多発血管炎性肉芽腫症患者にメポリズマブ 300mg を皮下投与した時の定常状態における血漿中メポリズマブ濃度（μg/mL）

	投与 28 週目 （トラフ値）	投与 29 週目
全体集団	32.2（9.98） (66 例)	45.5（8.81） (45 例)
日本人集団	31.1（6.75） 26.4，28.2，38.9 (3 例)	52.0（6.25） 48.0，48.7，59.2 (3 例)

上段：平均値（SD）、中段：各症例の血漿中メポリズマブ濃度（日本人集団のみ）、下段：（例数）

16.1.4 鼻茸を伴う慢性副鼻腔炎患者

鼻茸を伴う慢性副鼻腔炎患者にメポリズマブ 100mg を 4 週間ごとに皮下投与した時の定常状態における薬物動態パラメータの母集団薬物動態解析に基づく推定値を表 5 に示す。

表 5 鼻茸を伴う慢性副鼻腔炎患者にメポリズマブ 100mg を皮下投与した時の定常状態における薬物動態パラメータ（母集団薬物動態解析に基づく推定値）

薬物動態パラメータ	日本人（41 例）	外国人（15 例）
Cmax ss（μg/mL）	17.39（2.94）	17.44（5.86）
AUC ss（μg･day/mL）	371.48（71.75）	382.37（138.57）

平均値（SD）

16.1.5 相対的バイオアベイラビリティ

健康成人にヌーカラ皮下注 100mg シリンジ、ヌーカラ皮下注 100mg ペン及び凍結乾燥注射剤 100mg をそれぞれ単回皮下投与した [1)]。その結果、ヌーカラ皮下注 100mg シリンジ及びヌーカラ皮下注 100mg ペンの最高血漿中濃度（Cmax）及び最終測定時点までの血漿中濃度－時間曲線下面積（AUC_{0-t}）の凍結乾燥注射剤 100mg に対する比（90%信頼区間）は表 6 の通りであり、90%信頼区間はいずれも生物学的同等性の基準である 0.8～1.25 の範囲内であった（外国人データ）。

表 6 健康成人にヌーカラ皮下注 100mg シリンジ、ヌーカラ皮下注 100mg ペンを単回皮下投与した時の凍結乾燥注射剤 100mg に対する薬物動態パラメータの比

	Cmax	AUC_{0-t}
ヌーカラ皮下注 100mg シリンジ	1.06 (0.99，1.12)	1.04 (0.97，1.12)
ヌーカラ皮下注 100mg ペン	1.04 (0.98，1.11)	1.08 (1.01，1.15)

幾何平均値の比（90%信頼区間）

16.2 吸収

健康成人にメポリズマブ 250mg [注)] を上腕部に単回皮下投与した時の絶対的バイオアベイラビリティは 75%(90%信頼区間:65.6，86.4)であった。上腕部、大腿部又は腹部に単回皮下投与した時、投与部位間の絶対的バイオアベイラビリティの差は小さかった（外国人データ）。

16.4 代謝

メポリズマブはヒト化 IgG1 モノクローナル抗体であり、体内に広く分布する蛋白質分解酵素で分解されると推定される。

注）本剤の承認用量は気管支喘息では成人及び 12 歳以上の小児で 100mg、6 歳以上 12 歳未満の小児で 40mg、鼻茸を伴う慢性副鼻腔炎では 100mg、好酸球性多発血管炎性肉芽腫症では 300mg である。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈気管支喘息〉

17.1.1 国際共同第Ⅲ相試験（成人及び 12 歳以上の小児）

12 歳以上の重症喘息患者（高用量の吸入ステロイド薬及びその他の長期管理薬を併用しているが喘息増悪をきたす患者で、血中好酸球数が試験開始時に 150/μL 以上の患者、又は過去 12 ヵ月間に 300/μL 以上が認められた患者）576 例（日本人患者 50 例を含む）を対象にメポリズマブ凍結乾燥注射剤を用いて実施したプラセボ対照二重盲検比較試験において、既存治療に上乗せしてメポリズマブ 100mg を 4 週間ごとに皮下投与した時の 32 週間の投与期間における喘息増悪（全身性ステロイド薬による治療、入院、又は救急外来受診を必要とする喘息症状の悪化）の頻度を評価した [2)]。その結果、喘息増悪の頻度はメポリズマブ 100mg 群において 0.83 回/年、プラセボ群において 1.74 回/年であり、メポリズマブ 100mg

群はプラセボ群に比し有意に増悪頻度が少なかった(表1)。また、組入れ時及び投与開始時における血中好酸球数別の部分集団解析結果は表2及び表3の通りであった。[5.2参照]
本試験の治験薬投与期間における副作用発現頻度は、メポリズマブ100mg群で20%（39/194例）であった。主な副作用は、注射部位反応7%（14/194例）、頭痛4%（8/194例）及び疲労2%（4/194例）であった。

表1　喘息増悪の頻度

	メポリズマブ100mg群	プラセボ群
症例数	194	191
喘息増悪発現例数（割合）、件数	64（0.33）、116	105（0.55）、216
喘息増悪の頻度（回/年）注1)	0.83	1.74
プラセボ群に対する比注2)［95%信頼区間注1)］、p値注1)	0.47［0.35, 0.64］、p＜0.001	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル
注2）メポリズマブ100mg群/プラセボ群

表2　組入れ時（投与開始1～6週間前）における血中好酸球数別の喘息増悪の頻度

		メポリズマブ100mg群（194例）	プラセボ群（191例）
150/μL未満	症例数	35	21
	喘息増悪の頻度（回/年）注1)	1.20	1.31
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.91［0.44, 1.90］	
150/μL以上、300/μL未満	症例数	49	59
	喘息増悪の頻度（回/年）注1)	0.62	1.28
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.48［0.27, 0.86］	
300/μL以上、500/μL未満	症例数	45	48
	喘息増悪の頻度（回/年）注1)	0.78	1.63
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.48［0.26, 0.89］	
500/μL以上	症例数	61	60
	喘息増悪の頻度（回/年）注1)	0.47	2.26
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.21［0.12, 0.36］	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル
注2）メポリズマブ100mg群/プラセボ群

表3　投与開始時における血中好酸球数別の喘息増悪の頻度

		メポリズマブ100mg群（194例）	プラセボ群（191例）
150/μL未満	症例数	39	32
	喘息増悪の頻度（回/年）注1)	1.15	1.92
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.60［0.32, 1.13］	
150/μL以上、300/μL未満	症例数	53	51
	喘息増悪の頻度（回/年）注1)	0.67	1.02
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.66［0.34, 1.29］	
300/μL以上、500/μL未満	症例数	34	40
	喘息増悪の頻度（回/年）注1)	0.80	1.66
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.48［0.23, 1.00］	
500/μL以上	症例数	66	66
	喘息増悪の頻度（回/年）注1)	0.54	2.11
	プラセボ群に対する比注2)［95%信頼区間注1)］	0.25［0.15, 0.43］	

注1）投与期間の対数をオフセット変数、投与群、地理的地域、ベースライン時のFEV_1の予測値に対する割合、経口ステロイド薬の併用の有無及び治験開始前1年間における喘息増悪の頻度を共変量とし、負の2項確率分布を仮定した一般化線形モデル
注2）メポリズマブ100mg群/プラセボ群

17.1.2 国際共同第Ⅱ相試験（6歳以上12歳未満の小児）
6～11歳の小児重症喘息患者（高用量の吸入ステロイド薬及びその他の長期管理薬を併用しているが喘息増悪をきたす患者で、血中好酸球数が試験開始時に150/μL以上の患者、又は過去12ヵ月間に300/μL以上が認められた患者）36例（日本人患者7例を含む）を対象に実施した非対照非盲検試験において、既存治療に上乗せしてメポリズマブ凍結乾燥注射剤注1)を4週間ごとに12週間皮下投与した。8週間の休薬後、30例（日本人患者7例を含む）を対象にメポリズマブ凍結乾燥注射剤注2)を52週間皮下投与した3)。52週間の投与期間における喘息増悪（全身性ステロイド薬による治療、入院、又は救急外来受診を必要とする喘息症状の悪化）の頻度（回/年［95%信頼区間］）は、試験開始前12ヵ月間の発現回数（平均値）注3) 3.5回/年に対して1.09回/年［0.63, 1.89］であった。[5.2参照]
52週間の投与期間における副作用発現頻度は、メポリズマブ凍結乾燥注射剤群全体で27%（8/30例）であった。主な副作用は、頭痛13%（4/30例）、上腹部痛10%（3/30例）及び発熱7%（2/30例）であった注2)。
注1）初回投与時に体重が40kg未満の患者（26例）に対してはメポリズマブ凍結乾燥注射剤40mgを、40kg以上の患者（10例）に対してはメポリズマブ凍結乾燥注射剤100mgを投与した。なお、本剤の承認用量は6歳以上12歳未満の小児では40mgである。
注2）8週間の休薬後に体重が40kg未満の患者（16例）に対してはメポリズマブ凍結乾燥注射剤40mgを、40kg以上の患者（10例）に対してはメポリズマブ凍結乾燥注射剤100mgを投与した。ただし、来院ごとに体重を測定し、体重が40kgを超えた患者（4例）には、以降の投与量を100mgとした。
注3）全身性ステロイド薬による治療を必要とする喘息増悪の回数と定義した。

〈好酸球性多発血管炎性肉芽腫症〉
17.1.3 国際共同第Ⅲ相試験（18歳以上の成人）
18歳以上の再燃又は難治性の好酸球性多発血管炎性肉芽腫症患者136例（日本人患者6例を含む）を対象にメポリズマブ凍結乾燥注射剤を用いて実施したプラセボ対照二重盲検比較試験において、

経口ステロイド薬（プレドニゾロン換算で 7.5～50mg/日）[注1)]に追加[注2)]してメポリズマブ 300mg を 4 週間ごとに 52 週間皮下投与した[4)]。その結果、プラセボ群に比べメポリズマブ 300mg 群で累積寛解維持期間が有意に長く（表 4）、また投与 36 週時及び 48 週時の両時点において寛解状態にあった症例の割合は有意に高かった（表 5）。投与期間最後の 4 週間における経口ステロイド薬の平均 1 日用量は、メポリズマブ 300mg 群でプラセボ群よりも有意に低く、0mg となった症例はメポリズマブ 300mg 群 18%（12/68 例）、プラセボ群 3%（2/68 例）であった。[7.1 参照]

本試験の治験薬投与期間及び後観察期間（8 週間）における副作用発現頻度は、メポリズマブ 300mg 群で 51%（35/68 例）であった。主な副作用は、注射部位反応 10%（7/68 例）、頭痛 7%（5/68 例）、無力症及び気道感染各 6%（各 4/68 例）であった。

注 1）経口ステロイド薬は、医師の判断で投与開始 4 週以降に適宜減量することと設定した。

注 2）免疫抑制剤（シクロホスファミドを除く）は、併用可能とされた。

表 4　累積寛解維持期間

	メポリズマブ 300mg群 (68 例)	プラセボ群 (68 例)
累積寛解維持期間[注1)]別の症例数（割合）		
0 週	32（47%）	55（81%）
0 週超～12 週未満	8（12%）	8（12%）
12 週～24 週未満	9（13%）	3（4%）
24 週～36 週未満	10（15%）	0
36 週以上	9（13%）	2（3%）
プラセボ群に対するオッズ比[注2)] [95%信頼区間][注3)] p 値[注3)]	5.91 [2.68, 13.03] p＜0.001	

注 1）52 週間の投与期間のうちバーミンガム血管炎活動性スコア（BVAS）が 0、かつ経口ステロイド薬の平均 1 日用量が 4mg 以下の寛解状態にあった週数の累積期間

注 2）メポリズマブ 300mg 群/プラセボ群

注 3）ベースライン時の経口ステロイド薬の平均 1 日用量、BVAS、治療群及び地域を共変量とした順序カテゴリカルデータに対する比例オッズ回帰モデル

表 5　投与 36 週時及び 48 週時の両時点で寛解状態であった症例の割合

	メポリズマブ 300mg群 (68 例)	プラセボ群 (68 例)
寛解状態であった症例数（割合）[注1)]	22（32%）	2（3%）
プラセボ群に対するオッズ比[注2)] [95%信頼区間][注3)] p 値[注3)]	16.74 [3.61, 77.56] p＜0.001	

注 1）BVAS が 0、かつ経口ステロイド薬の 1 日用量が 4mg 以下の場合を寛解と定義し、投与 36 週時及び 48 週時の両時点で寛解状態であった症例の割合

注 2）メポリズマブ 300mg 群/プラセボ群

注 3）ベースライン時の経口ステロイド薬の平均 1 日用量、BVAS、治療群及び地域を共変量としたロジスティック回帰モデル

〈鼻茸を伴う慢性副鼻腔炎〉

17.1.4 国際共同第Ⅲ相試験（18 歳以上の成人）

手術又は全身性ステロイド薬の投与によっても効果不十分[注1)]な、18 歳以上の鼻茸を伴う慢性副鼻腔炎患者 163 例（日本人患者 85 例を含む）を対象にメポリズマブ液剤を用いて実施したプラセボ対照二重盲検比較試験において、標準治療[注2)]に追加してメポリズマブ 100mg を 4 週間ごとに 52 週間皮下投与した時の投与 52 週時の有効性評価項目の結果は表 6 のとおりであった。[5.5 参照]

52 週間の投与期間における副作用発現頻度は、メポリズマブ 100mg 群で 3%（2/80 例）であった。すべての副作用の発現頻度は 2%未満（1/80 例）であり、頭痛、顔面痛、疼痛、咳嗽、発声障害、口腔咽頭痛、アラニンアミノトランスフェラーゼ増加、骨痛であった。

注 1）鼻手術歴を有する、及び/又は鼻茸の治療のため過去 2 年以内に 3 日以上連続の全身性ステロイド薬投与がある、及び/又は全身性ステロイド薬に対する医学的禁忌/不耐性がある患者で、両側鼻茸スコアが 5 以上（各鼻腔スコアは 2 以上）、かつ鼻閉 VAS 症状スコアが 5 を超える。加えて、JESREC スコア 11 以上であること、血中好酸球数が 2%超 5%以下であると確認された患者については気管支喘息、アスピリン不耐症又は非ステロイド性抗炎症薬アレルギーの合併が必要であり、血中好酸球数が 5%超の患者については CT 陰影が篩骨洞≥上顎洞の場合、前出の合併を必要としない。

注 2）各国の診療方針に応じて、鼻腔内ステロイド（INCS）、生理食塩液による鼻腔内洗浄、全身性ステロイド薬及び/又は抗生物質の短期投与等

表 6　投与 52 週時におけるベースラインからの変化量の調整平均及び群間差

		メポリズマブ 100mg 群 (80 例)	プラセボ群 (83 例)
鼻茸スコア[注1)]	投与前[注2)]	5.9 (1.27)	6.1 (1.25)
	変化量[注3)]	-0.62 (0.164)	-0.19 (0.164)
	プラセボ群との差 [95%信頼区間][注4)] p 値[注4)]	-0.43 [-0.89, 0.03] 0.067	
鼻閉 VAS 症状スコア[注1)]	投与前[注2)]	8.60 (1.249)	8.59 (1.260)
	変化量[注3)]	-3.23 (0.336)	-1.80 (0.333)
	プラセボ群との差 [95%信頼区間][注4)] p 値[注4)]	-1.43 [-2.37, -0.50] 0.003	
LMK-CT スコア[注1)]	投与前[注2)]	20.3 (3.25)	20.7 (3.44)
	変化量[注3)]	-3.52 (0.449)	-1.88 (0.452)
	プラセボ群との差 [95%信頼区間][注4)]	-1.63 [-2.90, -0.37]	
SNOT-22 総スコア[注1)]	投与前[注2)]	56.9 (18.94)	55.6 (20.22)
	変化量[注3)]	-18.27 (2.889)	-7.65 (2.869)
	プラセボ群との差 [95%信頼区間][注4)]	-10.63 [-18.68, -2.57]	

注 1）鼻茸スコア（0-8 点）；鼻閉 VAS 症状スコア（0-10 点）；LMK-CT スコア（0-24 点）；SNOT-22 総スコア（0-110 点）
鼻茸スコア、鼻閉 VAS 症状スコア、LMK-CT スコア及び SNOT-22 総スコアはスコアの減少が改善を意味する。

注 2）平均値（SD）

注 3）投与 52 週時における調整平均（SE）

注 4）投与群、ベースライン値、ベースラインの血中好酸球数の対数値、標準治療としての INCS 使用、国及び時点を共変量とし、ベースライン値と時点及び投与群と時点の交互作用を考慮した MMRM（反復測定混合モデル解析）

18. 薬効薬理

18.1 作用機序

メポリズマブはヒトインターロイキン-5（IL-5）に対して特異的に結合し、好酸球の細胞表面に発現している IL-5 受容体α鎖への IL-5 結合を阻害することにより、IL-5 の好酸球増殖作用を抑制する。

18.2 好酸球に対する作用

メポリズマブの投与により、カニクイザルのアスカリス抗原誘発喘息モデルにおいて血中及び気管支肺胞洗浄液中の好酸球数が減少した[6)]。メポリズマブの投与により、重症喘息患者において血中好酸球数及び誘発喀痰中好酸球比率が減少した[2), 3), 7), 8)]。また、メポリズマブの投与により、好酸球性多発血管炎性肉芽腫症患者及び鼻茸を伴う慢性副鼻腔炎患者において血中好酸球数が減

少した[4),5)]。

19. 有効成分に関する理化学的知見

一般的名称：　メポリズマブ（遺伝子組換え）
Mepolizumab （Genetical Recombination）

本　　質：　メポリズマブは、遺伝子組換えヒト化モノクローナル抗体であり、マウス抗ヒトインターロイキン-5 抗体の相補性決定部、並びにヒト IgG1 のフレームワーク部及び定常部からなる。メポリズマブは、チャイニーズハムスター卵巣細胞により産生される。メポリズマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 本及び 220 個のアミノ酸残基からなる L 鎖（κ鎖）2 本で構成される糖タンパク質（分子量：約 149,000）である。

分 子 式：　$C_{6476}H_{10084}N_{1732}O_{2028}S_{46}$（糖鎖部分を含まない）

分 子 量：　約 149,000

20. 取扱い上の注意

凍結を避けて保存すること。冷蔵庫から取り出した場合は、室温(30℃以下)で外箱に入れたまま保存し、7 日以内に使用すること。また、外箱開封後は遮光して保存すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

〈ヌーカラ皮下注 100mg ペン〉
1mL[1ペン]

〈ヌーカラ皮下注100mgシリンジ〉
1mL[1シリンジ]

〈小児用ヌーカラ皮下注40mgシリンジ〉
0.4mL[1シリンジ]

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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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1.8.2. 効能又は効果及びその設定根拠

本申請に伴う追記内容を下線で示す。

1.8.2.1. 効能又は効果

効能又は効果

100mg ペン、100mg シリンジ
気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）
既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症
鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）

小児用 40mg シリンジ
気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）

効能又は効果に関連する使用上の注意

1. 気管支喘息
   1） 高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。
   2） 投与前の血中好酸球数が多いほど本剤の気管支喘息増悪発現に対する抑制効果が大きい傾向が認められている。また、データは限られているが、投与前の血中好酸球数が少ない患者では、十分な気管支喘息増悪抑制効果が得られない可能性がある。本剤の作用機序及び臨床試験で認められた投与前の血中好酸球数と有効性の関係を十分に理解し、患者の血中好酸球数を考慮した上で、適応患者の選択を行うこと（【臨床成績】の項参照）。
   3） 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。
2. 好酸球性多発血管炎性肉芽腫症
   過去の治療において、全身性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、本剤を上乗せして投与を開始すること。
3. 鼻茸を伴う慢性副鼻腔炎
   本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。（【臨床成績】の項参照）

1.8.2.2. 効能又は効果の設定根拠

欧米における鼻茸（NP）を伴う慢性副鼻腔炎（CRSwNP）と本邦における好酸球性副鼻腔炎（ECRS）は類似した病態を指し、特に重症の CRSwNP と重症の ECRS は、いずれも再発を繰り返す、極めて難治性で生活の質（QOL）の低下した病態を示していることから、両極における CRSwNP と ECRS の患者集団は広く重なると考えられる。

CRSwNP の治療は、欧米では主に鼻腔内ステロイド（INCS）と生理食塩水が用いられており、効果が不十分の場合には、経口ステロイド薬（OCS）及び内視鏡下鼻副鼻腔手術

（ESS）が用いられる[Fokkens, 2020]。本邦において慢性副鼻腔炎（CRS）には ESS もしくはマクロライド少量長期療法、ECRS には OCS が主に用いられ[藤枝, 2015b]、これらの疾患に対し承認はされていないものの、欧米と同様に INCS も使用されている[大久保, 2017]。近年、CRSwNP 及び ECRS において、疾患形成の分子機序を考慮した治療法を選択する動きが高まっており[竹野, 2018]、2020 年 3 月には、ヒト型抗ヒトインターロイキン（IL）-4/13 受容体モノクローナル抗体であるデュピルマブ（遺伝子組換え）が Type 2 炎症に作用する新たな治療選択肢として追加された。

メポリズマブ（遺伝子組換え）（以下、メポリズマブ）は、好酸球の分化、生存及び活性化に関与する主要なサイトカインである IL-5 に高い特異性及び親和性で結合する抗 IL-5 抗体であり、IL-5 を中和することで、血中及び NP 組織中の好酸球数を減少させる。CRSwNP／ECRS 患者の NP 組織中の主な炎症細胞は好酸球であり、疾患形成や重症化要因、更には予後にも関与すると考えられ、CRSwNP／ECRS において好酸球は病態の中心的な役割を担っている[Gevaert, 2011; Liu, 2020]。以上のことから、メポリズマブは CRSwNP／ECRS 治療において新たな選択肢となると考えた。

本申請における CRSwNP に関するメポリズマブの効能又は効果は、本邦から参加した CRSwNP 患者を対象とした国際共同試験（209692 試験）及び海外で実施した CRSwNP 患者を対象とした国際共同試験（205687 試験）の試験成績をもとに設定した。2.5.1.4.2.1 に示す民族的要因の考察に基づき、メポリズマブは民族的要因を受けにくい薬剤であり、209692 試験における薬物動態（PK）／薬力学（PD）において日本人集団と外国人集団で大きな差はみられず（2.7.2.5）、有効性及び安全性においても日本人集団と全体集団で大きな差はみられなかった（2.5.4.3.2.7.3、2.5.5.3.8.1.1.2）。以上のことから、日本人における PK、PD、有効性及び安全性は、209692 試験及び 205687 試験の試験成績を用いて評価することが可能であり、CRSwNP 患者の全体集団から設定した効能又は効果を日本人における効能又は効果として用いることができると考えた。

以下に、本邦における効能又は効果の設定根拠となった試験成績を記載する。

1.8.2.2.1. 効能又は効果の設定根拠となった臨床試験成績

209692 試験では、標準治療を受けているにもかかわらず手術の対象となる再発性、難治性の重度の CRSwNP 患者（18 歳以上）を組み入れ、メポリズマブを標準治療に追加投与した時の有効性及び安全性を検討した。

Co-primary endpoint である NP スコアの合計及び鼻閉視覚アナログ尺度（VAS）症状スコアにおいて、プラセボ群と比較してメポリズマブ群で改善が認められた（2.5.4.3.2.3）。また、Lund-Mackay（LMK）-CT スコア及び副鼻腔評価テスト-22 質問票（SNOT-22）総スコアをはじめとした全ての副次評価項目において、プラセボ群と比較してメポリズマブ群で改善が認められた（2.5.4.3.2.4）。

メポリズマブ投与による新たな安全性上の懸念は認められなかった。

205687 試験では、標準治療を受けているにもかかわらず再手術の対象となる再発性、難治性の重度の CRSwNP 患者（18 歳以上）を組み入れ、メポリズマブを標準的治療に追加投与した時の有効性及び安全性を検討した。

Co-primary endpoint である NP スコアの合計及び鼻閉 VAS 症状スコアにおいて、プラセボ群と比較してメポリズマブ群で統計学的に有意な改善が認められた。また、SNOT-22 総スコア及び初回の鼻手術までの時間をはじめとした全ての副次評価項目において、プラセボ群と比較してメポリズマブ群で統計学的有意な改善が認められた。

メポリズマブ投与による新たな安全性上の懸念は認められなかった。

以上より、CRSwNP を対象とした 209692 試験及び 205687 試験でメポリズマブの有効性が確認されたことから、メポリズマブの効能又は効果を「鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）」と設定した。

1.8.2.3. 効能又は効果に関連する使用上の注意の設定根拠

NP は術後の再発傾向が強く、多くの場合、数ヵ月から数年の間に再手術を要する。また、術後に NP を再発する患者の大部分が組織好酸球増多を伴う NP を有する患者であることが示唆されている[Brescia, 2015]。再手術の実施によって、手術の成功率が低下し副作用が生じる可能性が高くなることから[Bhattacharyya, 2004; Chu, 1997]、このような患者集団には別の治療選択肢が必要である。

209692 試験では、試験参加前の治療に関して下記の適格性基準を設定していたため、被験者は手術歴がない患者も含まれた。

- NP を除去するための NP 手術歴がある
- 過去 2 年以内に NP 治療を目的とした連続 3 日以上の全身性ステロイド薬の使用歴がある
- 全身性ステロイド薬に対する医学的禁忌／不耐性がある

過去の手術歴（0、1、2、>2 回）による部分集団解析において、メポリズマブの投与により概ね一貫した結果が得られており、手術歴の有無によらず有効性評価項目の改善がみられることが示された（2.7.3.2.1.5.3）。

以上のことから、「本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。（【臨床成績】の項参照）」を効能又は効果に関連する使用上の注意とした。

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1.8.3. 用法及び用量並びにその設定根拠

本申請に伴う追記内容を下線で示す。

1.8.3.1. 用法及び用量

用法及び用量

100 mg ペン、100 mg シリンジ

気管支喘息

通常、成人及び 12 歳以上の小児にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。

好酸球性多発血管炎性肉芽腫症

通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 300 mg を 4 週間ごとに皮下に注射する。

鼻茸を伴う慢性副鼻腔炎

通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。

小児用 40 mg シリンジ

気管支喘息

通常、6 歳以上 12 歳未満の小児にはメポリズマブ（遺伝子組換え）として 1 回 40 mg を 4 週間ごとに皮下に注射する。

用法及び用量に関連する注意

好酸球性多発血管炎性肉芽腫症

本剤とシクロホスファミドを併用投与した場合の安全性は確認されていない。（【臨床成績】の項参照）

鼻茸を伴う慢性副鼻腔炎

本剤による治療反応は、通常投与開始から 24 週までには得られる。24 週までに治療反応が得られない場合は、漫然と投与を続けないよう注意すること。

1.8.3.2. 設定根拠

1.8.3.2.1. 用法及び用量の設定根拠

鼻茸を伴う慢性副鼻腔炎（CRSwNP）における用法及び用量は、海外で実施した MPP111782 試験、205687 試験の試験成績及び母集団 PK 解析を基に設定し、その適切性を本邦から参加した 209692 試験の試験成績を基に検証した。以下に用法及び用量の設定根拠となる試験成績を示す。

- MPP111782 試験においてメポリズマブ 750 mg を 4 週毎に 24 週間静脈内投与したところ、標準治療を受けているにも関わらず再発性の鼻茸（NP）を有する患者において、手術の必要性の低下、NP の大きさの減少及び症状の改善が認められた（2.7.3.2.3）。メポリズマブ投与時の忍容性は良好で、プラセボと同様の安全性プロファイルを示した（2.7.4.2）。
- MPP111782 試験のデータを用いて、メポリズマブの血漿中濃度とインターロイキン（IL）-5 濃度、IL-5 濃度と血中好酸球数、血中好酸球数と NP スコアを関連付ける PK/PD モデルを構築した。構築した PK/PD モデルを用いて、メポリズマブの皮下投与における臨床的効果を検討したところ、100 mg 4 週間毎の皮下投与においても血中好酸球数は大きく減少し、NP スコア変化量で示される有効性が得られ、維持されることが予測された（2.7.2.3.2.1）。
- 205687 試験において、メポリズマブ 100 mg を 4 週毎に 52 週間皮下投与した際の血中好酸球数（幾何平均値）は、0.06 GI/L に減少することが臨床的に検証された（2.7.2.2.2.2）。また、メポリズマブ投与により NP の大きさの減少及び症状の改善が検証された（2.7.3.2.2.2）。メポリズマブ投与時の安全性は、既知の安全性プロファイルと同様で、新たな安全性上の懸念はみられなかった（2.7.4.2）
- 複数の試験及び疾患を併合した母集団 PK 解析の結果、臨床的に意味のある共変量は特定されず、民族や疾患は共変量として特定されなかった（2.7.2.3.1）。
- 209692 試験において、メポリズマブ 100 mg を 4 週毎に 52 週間皮下投与した際の血中好酸球数（幾何平均値）は 0.05 GI/L に減少することが臨床的に認められた（2.7.2.2.1.2）。また、メポリズマブ投与により NP の大きさの減少及び症状の改善が認められた（2.7.3.2.1.2）。メポリズマブ投与時の安全性は、MPP111782 試験及び 205687 試験でみられた安全性プロファイルと同様で、新たな安全性上の懸念はみられなかった（2.5.5.3.14）。

4 週間の投与間隔は、メポリズマブの半減期が 3 週間であること[Smith, 2011]及び 205687 試験でメポリズマブ 100 mg 皮下投与により治療期間を通して血中好酸球数の減少が持続したこと（2.7.2.2.2.2）から設定された。

209692 試験で 4 週毎にメポリズマブ 100 mg を皮下投与した際のプラセボ群に対する血中好酸球数の減少率は 83～88%であり、治療期間を通して血中好酸球数の減少が持続した（2.7.2.2.1.2）。これらのことから、4 週間毎の投与が適切であると考えられた。

以上のことから、CRSwNP に対する用法及び用量は、成人患者において 1 回 100 mg を 4 週間毎に皮下投与することが適切と考えられた。

1.8.3.2.2. 日本人における用法及び用量の設定根拠

メポリズマブは民族的要因による影響を受けにくい薬剤である（2.5.1.4.2.1）。また、209692 試験における PK／PD において日本人集団と外国人集団で大きな差はみられず

（2.7.2.5）、有効性及び安全性においても日本人集団と全体集団で大きな差はみられなかった（2.7.3.3.4.2、2.7.4.5.1.4）。

以上のことから、メポリズマブ全体の臨床開発プログラムにおける試験成績を日本人集団に適用することが可能と考えられ、海外と同様に本邦での用法及び用量を、「通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。」と設定した。

1.8.3.2.3. 用法及び用量に関連する注意の設定根拠

209692 試験成績より、メポリズマブ投与開始から 24 週時点までに改善傾向がみられ、投与開始から 52 週時点において更なるメポリズマブのベネフィットが認められることが示された（2.7.3.2.1）。

また、European Position Paper on Rhinosinusitis and Nasal Polyps（EPOS）／European Forum for Research and Education in Allergy and Airway Diseases（EUFOREA）の CRSwNP における生物学的製剤の適応と評価に関する 2023 年最新のレポート[Fokkens, 2023]によると、生物学的製剤における治療反応の評価時期については 6 ヵ月で評価し、1 年後に 2 回目の再評価が必要であると提言している。

以上のことから、CRSwNP 患者に対するメポリズマブの効果判定時期としてはメポリズマブ投与開始後 24 週目（投与開始から 6 ヵ月後）が適切であり、6 ヵ月時点で患者及び医師によりメポリズマブによる改善傾向が認められる場合は投与を継続し、メポリズマブの有効性が最大限に発揮されると推測される 52 週目（メポリズマブの投与開始から 12 ヵ月後）に再度効果判定を行うことが適切であることから、「本剤による治療反応は、通常投与開始から 24 週までには得られる。24 週までに治療反応が得られない場合は、漫然と投与を続けないよう注意すること。」を用法及び用量に関連する注意とした。

参考文献

Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. Rhinology. 2023;61(3):194-202.

Smith DA, Minthorn EA, Beerahee M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. Clin Pharmacokinet.2011; 50(4): 215-27

1.8.4. 使用上の注意（案）及びその設定根拠

使用上の注意（案）はヌーカラ皮下注 100 mg ペン/シリンジ、小児用ヌーカラ皮下注 40 mg シリンジの電子化された添付文書（電子添文）の内容に今回申請する「鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）」にかかわる注意を加えたものである。なお、最新のヌーカラ皮下注 100 mg ペン/シリンジ、小児用ヌーカラ皮下注 40 mg シリンジの電子添文（2023 年 12 月改訂：第 5 版）より変更する部分を下線（__部）にて示した。

使用上の注意（案）	設定根拠
2.禁忌（次の患者には投与しないこと） 本剤の成分に対し過敏症の既往歴のある患者	2023 年 12 月改訂：第 5 版電子添文から変更なし。
5.効能又は効果に関連する注意 **〈気管支喘息〉** **5.1** 高用量の吸入ステロイド薬とその他の長期管理薬を併用しても、全身性ステロイド薬の投与等が必要な喘息増悪をきたす患者に本剤を追加して投与すること。 **5.2** 投与前の血中好酸球数が多いほど本剤の気管支喘息増悪発現に対する抑制効果が大きい傾向が認められている。また、データは限られているが、投与前の血中好酸球数が少ない患者では、十分な気管支喘息増悪抑制効果が得られない可能性がある。本剤の作用機序及び臨床試験で認められた投与前の血中好酸球数と有効性の関係を十分に理解し、患者の血中好酸球数を考慮した上で、適応患者の選択を行うこと。［17.1.1、17.1.2 参照］ **5.3** 本剤は既に起きている気管支喘息の発作や症状を速やかに軽減する薬剤ではないので、急性の発作に対しては使用しないこと。 **〈好酸球性多発血管炎性肉芽腫症〉** **5.4** 過去の治療において、全身性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、本剤を上乗せして投与を開始すること。 **〈鼻茸を伴う慢性副鼻腔炎〉** **5.5** 本剤は全身性ステロイド薬、手術等ではコントロールが不十分な患者に用いること。［17.1.4 参照］	5.5 項を除き、2023 年 12 月改訂：第 5 版電子添文から変更なし。 5.5 項については、209692 試験の対象患者及び試験成績より設定した。
7. 用法及び用量に関連する注意 **〈好酸球性多発血管炎性肉芽腫症〉** **7.1** 本剤とシクロホスファミドを併用投与した場合の安全性は確認されていない。［17.1.3 参照］	7.2 項を除き、2023 年 12 月改訂：第 5 版電子添文から変更なし。

使用上の注意（案）	設定根拠
〈鼻茸を伴う慢性副鼻腔炎〉 **7.2** 本剤による治療反応は、通常投与開始から 24 週までには得られる。24 週までに治療反応が得られない場合は、漫然と投与を続けないよう注意すること。	7.2 項については、209692 試験の試験成績より設定した。
8. 重要な基本的注意 **8.1** 本剤の投与は、適応疾患の治療に精通している医師のもとで行うこと。 **8.2** 本剤はヒトインターロイキン-5（IL-5）と結合し、IL-5 の機能を阻害することにより血中好酸球数を減少させる。好酸球は一部の寄生虫（蠕虫）感染に対する免疫応答に関与している可能性がある。患者が本剤投与中に蠕虫類に感染し、抗蠕虫薬による治療が無効な場合には、本剤投与の一時中止を考慮すること。［9.1.1 参照］ **8.3** 長期ステロイド療法を受けている患者において、本剤投与開始後にステロイド薬を急に中止しないこと。ステロイド薬の減量が必要な場合には、医師の管理下で徐々に行うこと。 **8.4** 本剤の投与期間中に喘息に関連した事象及び喘息の悪化が現れることがある。本剤の投与開始後に喘息症状がコントロール不良であったり、悪化した場合には、医師の診察を受けるよう患者に指導すること。 **8.5** 本剤の投与によって合併する他の好酸球関連疾患の症状が変化する可能性があり、当該好酸球関連疾患に対する適切な治療を怠った場合、症状が急激に悪化し、喘息等では死亡に至るおそれもある。本剤の投与中止後の疾患管理も含めて、本剤投与中から、合併する好酸球関連疾患を担当する医師と適切に連携すること。患者に対して、医師の指示なく、それらの疾患に対する治療内容を変更しないよう指導すること。 **8.6** 本剤の投与開始にあたっては、医療施設において、必ず医師によるか、医師の直接の監督の下で投与を行うこと。自己投与の適用については、医師がその妥当性を慎重に検討し、十分な教育訓練を実施した後、本剤投与による危険性と対処法について患者又はその保護者が理解し、患者又はその保護者自ら確実に投与できることを確認した上で、医師の管理指導の下で実施すること。自己投与の適用後、本剤による副作用が疑われる場合や自己投与の継続が困難な状況となる可能性がある場合には、直ちに自己投与を中止し医療施設に連絡するよう患者又はその保護者に指導し、医師の管理下で慎重に観察するなど適切な処置を行うこと。また、使用済みの注射器を再使用しないように患者又はその保護	8.5 項を除き、2023 年 12 月改訂：第 5 版電子添文から変更なし。 8.5 項については、他の好酸球関連疾患を合併している患者では、本剤投与中止後に、本剤により症状が安定化していた合併症の好酸球関連疾患が悪化する可能性があることから設定した。

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>者に注意を促し、安全な廃棄方法について指導すること。</td><td></td></tr>
<tr><td>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 蠕虫類に感染している患者
本剤投与開始前に蠕虫感染を治療すること。［8.2 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。サルではメポリズマブが胎盤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。サルではメポリズマブが乳汁中へわずかに移行することが報告されている。
9.7 小児等
〈気管支喘息〉
9.7.1 6 歳未満の小児等を対象とした臨床試験は実施していない。
〈好酸球性多発血管炎性肉芽腫症、鼻茸を伴う慢性副鼻腔炎〉
9.7.2 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
一般に、生理機能が低下している。</td><td>9.7.2 項の記載整備を除き、2023 年 12 月改訂：第 5 版電子添文から変更なし。

9.7.2 項については、小児を対象とした鼻茸を伴う慢性副鼻腔炎の臨床試験は実施していないことから設定した。</td></tr>
<tr><td>11.副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。
11.1 重大な副作用
アナフィラキシー（頻度不明）
11.2 その他の副作用
<table>
<tr><th></th><th>5%以上</th><th>1%以上 5%未満</th><th>1%未満</th></tr>
<tr><td>過敏症</td><td></td><td>過敏症反応（蕁麻疹、血管性浮腫、発疹、気管支痙攣、低血圧）</td><td></td></tr>
<tr><td>感染症</td><td></td><td></td><td>下気道感染症、咽頭炎、尿路感染</td></tr>
<tr><td>精神神経系</td><td>頭痛</td><td></td><td></td></tr>
</table>
</td><td>副作用発現頻度の再集計を除き、2023 年 12 月改訂：第 5 版電子添文から変更なし。

鼻茸を伴う慢性副鼻腔炎を対象とした臨床試験の結果を合算し、副作用発現頻度を再集計した。</td></tr>
</table>

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>
<table>
<tr><td>呼吸器</td><td></td><td></td><td>鼻閉</td></tr>
<tr><td>胃腸障害</td><td></td><td></td><td>上腹部痛</td></tr>
<tr><td>皮膚</td><td></td><td></td><td>湿疹</td></tr>
<tr><td>筋骨格系</td><td></td><td></td><td>背部痛</td></tr>
<tr><td>全身障害</td><td></td><td></td><td>発熱</td></tr>
<tr><td>投与部位</td><td>注射部位反応（疼痛、紅斑、腫脹、そう痒、灼熱感）</td><td></td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td>14.適用上の注意
14.1 薬剤交付時の注意
患者又はその保護者には本剤に添付の使用説明書を渡し、使用方法を指導すること。
14.2 薬剤投与前の注意
14.2.1 投与前に室温で最低 30 分放置する。
14.2.2 開封後、8 時間以内に投与する。8 時間以内に投与しなかった場合は廃棄すること。
14.3 薬剤投与時の注意
〈効能共通〉
14.3.1 注射部位は上腕部、大腿部又は腹部とすること。
14.3.2 本剤は 1 回使用の製剤であり、1 回に全量を使用し再使用しないこと。使用後は針が格納されるため、分解しないこと。
〈好酸球性多発血管炎性肉芽腫症〉
14.3.3 100mg ずつ 3 ヵ所に分けて投与し、各注射部位は 5cm 以上離すこと。</td><td>2023 年 12 月改訂：第 5 版電子添文から変更なし。</td></tr>
</table>

1.10. 毒薬・劇薬等の指定審査資料のまとめ

＜現行＞

<table>
<tr><td>化学名・別名</td><td>メポリズマブは、遺伝子組換えヒト化モノクローナル抗体であり、マウス抗ヒトインターロイキン-5 抗体の相補性決定部、並びにヒト IgG1 のフレームワーク部及び定常部からなる。メポリズマブは、チャイニーズハムスター卵巣細胞により産生される。メポリズマブは、449 個のアミノ酸残基からなる H 鎖（γ1 鎖）2 本及び 220 個のアミノ酸残基からなる L 鎖（κ 鎖）2 本で構成される糖タンパク質（分子量：約 149,000）である。
別名：メポリズマブ（遺伝子組換え）及びその製剤</td></tr>
<tr><td>構造式</td><td>アミノ酸配列及び主な糖鎖の推定構造を次頁以降に示す。</td></tr>
<tr><td>効能・効果</td><td>気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る）
既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症</td></tr>
<tr><td>用法・用量</td><td>気管支喘息
通常、成人及び 12 歳以上の小児にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。

好酸球性多発血管炎性肉芽腫症
通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 300 mg を 4 週間ごとに皮下に注射する。</td></tr>
<tr><td>劇薬等の指定</td><td>原薬及び製剤：劇薬</td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：メポリズマブ（遺伝子組換え）
製剤：ヌーカラ皮下注 100 mg シリンジ、ヌーカラ皮下注 100 mg ペン（1 シリンジ又は 1 ペン（1 mL）中メポリズマブ（遺伝子組換え）100 mg 含有）</td></tr>
<tr><td>毒性</td><td>単回投与　概略の致死量（mg/kg）　静脈内
サル ♂♀　＞304

反復投与
<table>
<tr><th>動物種</th><th>投与期間</th><th>投与経路</th><th>投与量</th><th>無毒性量（mg/kg）</th><th>主な所見（mg/kg）</th></tr>
<tr><td>サル</td><td>6 ヵ月（1 ヵ月間隔、計 7 回）</td><td>静脈内</td><td>10, 100</td><td>♂♀100</td><td>≥10：血中好酸球数減少（薬理作用）</td></tr>
<tr><td>サル</td><td>6 ヵ月（1 ヵ月間隔、計 7 回）</td><td>皮下</td><td>10</td><td>♂♀10</td><td>10：血中好酸球数減少（薬理作用）</td></tr>
</table></td></tr>
</table>

副作用	【気管支喘息の場合】 重症喘息患者を対象とした 2 つの国際共同第 III 相臨床試験 （MEA115588 試験及び MEA115575 試験において、本剤 100 mg を皮下投与された 263 例（日本人 17 例を含む）を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 100 mg 皮下投与群　60/263 例（23%） 副作用（臨床検査値異常を含む）の種類： 100 mg 皮下投与群　注射部位反応　21 例 頭痛　14 例 過敏症　6 例 等 【好酸球性多発血管炎性肉芽腫症の場合】 好酸球性多発血管炎性肉芽腫症患者を対象とした国際共同第 III 相試験 （MEA115921 試験において、本剤 300 mg を投与された 68 例（日本人 3 例を含む）を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 300 mg 皮下投与群　35/68 例（51%） 副作用（臨床検査値異常を含む）の種類： 300 mg 皮下投与群　注射部位反応　7 例 頭痛　5 例 無力症　4 例 気道感染　4 例 等
会社	グラクソ・スミスクライン株式会社、製剤：輸入

アミノ酸配列及びジスルフィド結合：

L鎖

DIVMTQSPDS LAVSLGERAT INCKSSQSLL NSGNQKNYLA WYQQKPGQPP
KLLIYGASTR ESGVPDRFSG SGSGTDFTLT ISSLQAEDVA VYYCQNVHSF
PFTFGGGTKL EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC
EVTHQGLSSP VTKSFNRGEC

H鎖

QVTLRESGPA LVKPTQTLTL TCTVSGFSLT SYSVHWVRQP PGKGLEWLGV
IWASGGTDYN SALMSRLSIS KDTSRNQVVL TMTNMDPVDT ATYYCARDPP
SSLLRLDYWG RGTPVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV
YTLPPSREEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK

H鎖Q1：部分的ピログルタミン酸；H鎖N299：糖鎖結合；H鎖K449：部分的プロセシング
L鎖C220－H鎖C222，H鎖C228－H鎖C228，H鎖C231－H鎖C231：ジスルフィド結合

図 1.10-1　メポリズマブ（遺伝子組換え）のアミノ酸配列

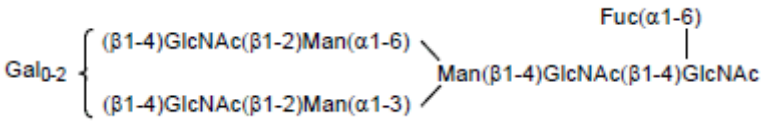


図 1.10-2　主な糖鎖の推定構造

＜追加＞

化学名・別名	
構造式	
効能・効果	気管支喘息（既存治療によっても喘息症状をコントロールできない難治の患者に限る） 既存治療で効果不十分な好酸球性多発血管炎性肉芽腫症 鼻茸を伴う慢性副鼻腔炎（既存治療で効果不十分な患者に限る）
用法・用量	気管支喘息 通常、成人及び 12 歳以上の小児にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。 好酸球性多発血管炎性肉芽腫症 通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 300 mg を 4 週間ごとに皮下に注射する。 鼻茸を伴う慢性副鼻腔炎 通常、成人にはメポリズマブ（遺伝子組換え）として 1 回 100 mg を 4 週間ごとに皮下に注射する。
劇薬等の指定	
市販名及び有効成分・分量	
毒性	
副作用	【気管支喘息の場合】 重症喘息患者を対象とした 2 つの国際共同第 III 相臨床試験（MEA115588 試験及び MEA115575 試験において、本剤 100 mg を皮下投与された 263 例（日本人 17 例を含む）を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 100 mg 皮下投与群　60/263 例（23%） 副作用（臨床検査値異常を含む）の種類： 100 mg 皮下投与群　注射部位反応　21 例 頭痛　14 例 過敏症　6 例 等 【好酸球性多発血管炎性肉芽腫症の場合】 好酸球性多発血管炎性肉芽腫症患者を対象とした国際共同第 III 相試験（MEA115921 試験において、本剤 300 mg を投与された 68 例（日本人 3 例を含む）を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 300 mg 皮下投与群　35/68 例（51%） 副作用（臨床検査値異常を含む）の種類： 300 mg 皮下投与群　注射部位反応　7 例 頭痛　5 例 無力症　4 例 気道感染　4 例 等

	【鼻茸を伴う慢性副鼻腔炎の場合】 鼻茸を伴う慢性副鼻腔炎患者を対象とした国際共同第 III 相試験 （209692 試験において、本剤 100 mg を投与された 80 例（日本人 41 例を含む）を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 100 mg 皮下投与群　2/80 例（3%） 副作用（臨床検査値異常を含む）の種類： 100 mg 皮下投与群 頭痛　1 例 顔面痛　1 例 疼痛　1 例 咳嗽　1 例 発声障害　1 例 口腔咽頭痛　1 例 アラニンアミノトランスフェラーゼ増加　1 例 骨痛　1 例 鼻茸を伴う慢性副鼻腔炎患者を対象とした海外第 III 相試験 （205687 試験において、本剤 100 mg を投与された 206 例を母集団とした。） 副作用（臨床検査値異常を含む）発現率： 100 mg 皮下投与群　30/206 例（15%） 副作用（臨床検査値異常を含む）の種類： 100 mg 皮下投与群 頭痛　8 例 紅斑　3 例 注射部位疼痛　3 例 上咽頭痛　3 例 等
会社	

下線部追加

1.12. 添付資料一覧

1.12.1. 添付資料一覧

添付資料はすべて社内資料を用いているため、著者欄は削除した。

第4部（試験報告書）
4.3. 参考文献　4.3.1. 参考文献一覧参照

第5部（臨床試験報告書）

添付資料番号	タイトル	試験実施期間	治験依頼者	報種類	掲載誌	評価／参考	申請電子データの提出有無
5.3.1.4							
2019N399870_00	Validation of an ELISA Method for the Quantification of SB240563 in Human Plasma (Assay Range 50.0 - 5000 ng/mL)	2019年4月～2019年7月	[redacted]（中国）	海外	社内資料	評価	無
2018N381947_00	Validation of an Electrochemiluminescence-Based Method for the Detection of Anti-SB-240563 Neutralizing Antibodies in Human Serum	2018年4月～2018年7月	[redacted]（米国）	海外	社内資料	評価	無
2022n511284_00	Validation of an Electrochemiluminescent-Based Method for the Detection of Anti-SB240563 Neutralizing Antibodies in Human Serum (Addendum 1 for 2018n381947)	2018年10月～2019年5月	[redacted]（米国）	海外	社内資料	評価	無
2021n467943_00	Validation of an Electrochemiluminescent Assay for the Detection of Anti-SB240563 Neutralizing Antibodies in Human Serum (Addendum 2 for 2018n381947)	2021年2月～2021年2月	[redacted]（米国）	海外	社内資料	評価	無
2019N399871_00	Method Validation Report for the Detection of Anti-SB240563 Antibodies in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA) Using the Meso-Scale Discovery (MSD) Platform	2019年4月～2019年7月	[redacted]（中国）	海外	社内資料	評価	無
2022N513220_00	Method Validation Report for the Detection of Anti-SB240563 Antibodies in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA) Using the Meso-Scale Discovery (MSD) Platform (Long-term Stability)	2019年4月～2020年4月	[redacted]（中国）	海外	社内資料	評価	無

添付資料番号	タイトル	試験実施期間	治験依頼者	報種類	掲載誌	評価／参考	申請電子データの提出有無
2022N513230_00	Method Validation Report for the Detection of Anti-SB240563 Antibodies in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA) Using the Meso-Scale Discovery (MSD) Platform (Confirmatory Cut Point)	2019年4月～2022年6月	[redacted]（中国）	海外	社内資料	評価	無
2021n483626_00	Determination of Anti-SB240563 (Mepolizumab) Neutralization Antibodies in Human Serum by Competitive LBA Method Using the Meso-Scale Discovery (MSD) Platform	2020年9月～2020年11月	[redacted]（中国）	海外	社内資料	評価	無
2020N431368_00	Quantification of SB-240563 in Human Lithium Heparin Plasma Samples From Clinical Study 205687 Using a Validated ELISA Method	2018年5月～2020年1月	[redacted]（米国）	海外	社内資料	評価	無
2015N263183_00	Quantification of SB-240563 in Heparin Human Plasma from Clinical Study MPP111782 Using ELISA	2011年4月～2015年2月	[redacted]（米国）	海外	社内資料	評価	無
2023N534405_00	Quantification of SB-240563 in Human Plasma Samples From Sponsor Clinical Study 209692 Using a Validated Enzyme-Linked Immunosorbent Assay Based Method	2022年3月～2023年4月	[redacted]（米国）	海外	社内資料	評価	無
2022N523838_00	Determination of SB240563 in human plasma with an ELISA method in support of the clinical trial 209692	2022年11月～2023年4月	[redacted]（中国）	海外	社内資料	評価	無
2020N430596_00	Detection of Anti-drug (SB240563) Antibodies in Human Serum by MSD for GSK Clinical Study (MPP111782)	2014年11月～2015年2月	GSK（米国）	海外	社内資料	評価	無
2020N431369_00	Detection of Anti-SB240563 Antibodies Using an Electrochemiluminescence Immunoassay (Meso Scale Discovery Platform) in Serum Samples From Subjects Enrolled in Clinical Study 205687	2019年2月～2020年1月	[redacted]（米国）	海外	社内資料	評価	無
2023N529323_00	Detection of Anti-SB240563 Antibodies Using an Electrochemiluminescence Immunoassay (Meso Scale Discovery Platform) in Serum Samples From Subjects Enrolled in Clinical Study 209692	2022年3月～2023年4月	[redacted]（米国）	海外	社内資料	評価	無
2023N529312_00	Bioanalytical Report for the Determination of Anti-SB240563 Antibodies in Human Serum using Bridging ECLA on MSD Platform, in support of Clinical Trial 209692	2023年3月～2023年4月	[redacted]（中国）	海外	社内資料	評価	無
2020N430597_00	Detection of Neutralizing Anti-drug (SB240563) Antibodies in Human Serum Samples by MSD for GSK Clinical Study (MPP111782)	2014年12月～2015年1月	GSK（米国）	海外	社内資料	評価	無
2020N431370_00	Detection of Anti-SB240563 Neutralizing Antibodies in Human Serum Samples from Sponsor Clinical Study 205687 Using a Validated Electrochemiluminescence-Based Method	2019年12月～2019年12月	[redacted]（米国）	海外	社内資料	評価	無

添付資料番号	タイトル	試験実施期間	治験依頼者	報種類	掲載誌	評価／参考	申請電子データの提出有無
2023N529324_00	Detection of Anti-SB240563 Neutralizing Antibodies in Human Serum Samples from Sponsor Clinical Study 209692 Using a Validated Electrochemiluminescence-Based Method	2023年5月～2023年5月	[redacted]（米国）	海外	社内資料	評価	無
2023N529313_00	Bioanalytical Report for Immunogenicity Evaluation of Anti-SB240563 (Mepolizumab) Neutralization Antibodies in support of Clinical Trial 209692	2023年5月～2023年5月	[redacted]（中国）	海外	社内資料	評価	無
5.3.3.5							
2018n368706	The relationship between blood eosinophil count and clinical efficacy in subjects with nasal polyposis and severe asthma	2018年5月報告	GlaxoSmithKline	海外	社内資料	参考	有
5.3.5.1							
209692	A randomised, double-blind, placebo controlled, parallel group Phase III study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS) MERIT: Mepolizumab in Eosinophilic chronic RhinosinusITis study	2021年2月8日～2023年4月12日	GlaxoSmithKline	海外	社内資料	参考	有
209692-amend1	209692 (Amendment 1)：A randomised, double-blind, placebo controlled, parallel group Phase III study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS) MERIT: Mepolizumab in Eosinophilic chronic RhinosinusITis study	2021年2月8日～2023年4月12日	GlaxoSmithKline	海外	社内資料	評価	有
205687	A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)	2017年5月25日～2019年12月11日	GlaxoSmithKline	海外	社内資料	評価	有
111782	A Randomised, Double blind, Placebo Controlled, Multi-centre Study to Investigate the Use of Mepolizumab (SB240563) in Reducing the Need for Surgery in Subjects with Severe Bilateral Nasal Polyposis	2009年5月12日～2014年12月5日	GlaxoSmithKline	海外	社内資料	評価	有
5.3.5.3							
－	ISS Data Displays	－	GlaxoSmithKline	海外	社内資料	参考	有
2014N216074_01	Integrated Summary of Immunogenicity for Mepolizumab	－	GlaxoSmithKline	海外	社内資料	参考	無

添付資料番号	タイトル	試験実施期間	治験依頼者	報種類	掲載誌	評価／参考	申請電子データの提出有無
5.3.5.4							
MEA115921	MEA115921 additional safety analysis	－	GlaxoSmithKline	海外	社内資料	参考	無
5.3.6							
－	PBRER Mepolizumab (17 Nov 2021 to 16 Nov 2022)	2021年11月17日～2022年11月16日	GlaxoSmithKline	海外	社内資料	参考	無
－	PMS additional safety analysis (204524_asthma)	2017年1月～2023年9月	GlaxoSmithKline	国内	社内資料	参考	無
－	PMS additional safety analysis (208505_EGPA)	2018年5月～継続中	GlaxoSmithKline	国内	社内資料	参考	無
－	PMS additional safety analysis reporting plan(204524/208505)	－	GlaxoSmithKline	国内	社内資料	参考	無

5.4. 参考文献　5.4.1. 参考文献一覧参照

1.12.2. 提出すべき資料がない項目一覧

第3部 （品質に関する文書）

第4部
4.3 参考文献以外は提出なし

第5部のうち、以下の項目

5.3.1.1	バイオアベイラビリティ（BA）試験報告書
5.3.1.2	比較BA試験及び生物学的同等性（BE）試験報告書
5.3.1.3	In Vitro-In Vivoの関連を検討した試験報告書
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
5.3.3.1	健康被験者におけるPK及び初期忍容性試験報告書
5.3.3.2	患者におけるPK及び初期忍容性試験報告書
5.3.3.3	内因性要因を検討したPK試験報告書
5.3.3.4	外因性要因を検討したPK試験報告書
5.3.4	臨床薬力学(PD)試験報告書
5.3.5.2	非対照試験報告書