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

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

Dosage and Administration, Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe (2.4)	6/2019

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

NUCALA is an interleukin-5 (IL-5) antagonist monoclonal antibody (IgG1 kappa) indicated for:

- Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1.1)
- The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). (1.2)

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

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

- Asthma: 100 mg administered subcutaneously once every 4 weeks. (2.1)
- EGPA: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks. (2.2)

---------- 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)

---------- 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%) include headache, injection site reaction, back pain, and fatigue. (6.1)

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: 6/2019

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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 patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14.1)]*.

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Limitations of Use

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

1.2 Eosinophilic Granulomatosis with Polyangiitis

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

2 DOSAGE AND ADMINISTRATION

NUCALA is for subcutaneous (SC) use only.

2.1 Severe Asthma

The recommended dosage of NUCALA is 100 mg administered once every 4 weeks by SC injection into the upper arm, thigh, or abdomen.

2.2 Eosinophilic Granulomatosis with Polyangiitis

The recommended dosage of NUCALA is 300 mg administered once every 4 weeks by SC injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen. It is recommended that the individual 100-mg injections be administered at least 5 cm (approximately 2 inches) apart if more than 1 injection is administered at the same site. *[See Dosage and Administration (2.3)]*.

Preparation of the 300-mg dose for treatment of EGPA requires the reconstitution of 3 separate 100-mg vials or administration of 3 prefilled autoinjectors or 3 prefilled syringes as described below *[see Dosage and Administration (2.3, 2.4)]*.

2.3 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 cake. 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.

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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.

<u>Administration</u>

1. For SC 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.

2.4 Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe

NUCALA injection is intended for use under the guidance of a healthcare provider. A patient may self-inject or the patient caregiver may administer NUCALA injection subcutaneously after the healthcare provider determines it is appropriate. Provide proper training in SC injection technique and on the preparation and administration of NUCALA injection prior to use according to the “Instructions for Use”.

1. Remove the prefilled autoinjector or prefilled syringe from the refrigerator and allow it to sit at room temperature for approximately 30 minutes prior to injection. Do not warm NUCALA 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.

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3. Administer the SC injection into the thigh or abdomen, avoiding the 5 cm (2 inches) around the navel. The upper arm can also be used if a caregiver administers the SC injection.
4. For use in EGPA, ensure injection sites for each SC injection are separated by at least 5 cm (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 or a single-dose prefilled glass syringe.

4 CONTRAINDICATIONS

NUCALA should not be administered to patients with a history of hypersensitivity to mepolizumab or excipients in the formulation *[see 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.

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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

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trials 1, 2, and 3). 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 subjects 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 subjects had markers of eosinophilic airway inflammation *[see Clinical Studies (14.1)]*. Of the subjects 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 subjects received NUCALA (mepolizumab 100 mg SC) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

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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 Subjects with 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 subjects receiving mepolizumab 75 mg IV compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In Trials 1, 2, and 3 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 5% in the placebo group and 3% in the group receiving NUCALA 100 mg. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA 100 mg. 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 subjects in the group receiving NUCALA 100 mg and 3% of subjects in the placebo group. The most commonly reported manifestations of

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systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in subjects 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 subjects receiving NUCALA 100 mg compared with 3% in subjects receiving placebo.

Long-term Safety

Nine hundred ninety-eight subjects 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 asthma trials described above.

6.2 Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 subjects with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Subjects received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Subjects 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 (14.2)]*. Of the subjects 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 subjects who experienced systemic (allergic and non-allergic) reactions was 1% in the placebo group and 6% in the group receiving 300 mg of NUCALA. Systemic allergic/hypersensitivity reactions were reported by 1% of subjects in the placebo group and 4% of subjects in the group receiving 300 mg of NUCALA. 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%) subject in the group receiving 300 mg of NUCALA and no subjects 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 subjects 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 subjects receiving NUCALA compared with 13% in subjects receiving placebo.

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6.3 Immunogenicity

In subjects with asthma receiving NUCALA 100 mg, 15/260 (6%) developed anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 subject 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 subjects with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any subjects with EGPA.

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.

6.4 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.

<u>Immune System Disorders</u>

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

<u>Pregnancy Exposure Registry</u>

There is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-311-8972 or visiting www.mothertobaby.org/asthma.

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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 SC *(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

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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

The safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. A total of 28 adolescents aged 12 to 17 years with asthma were enrolled in the Phase 3 asthma studies. Of these, 25 were enrolled in the 32-week exacerbation trial (Trial 2) and had a mean age of 14.8 years. Subjects had 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 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).]* Subjects had a reduction in the rate of exacerbations that trended in favor of mepolizumab. Of the 19 adolescents who received mepolizumab, 9 received NUCALA 100 mg and the mean apparent clearance in these subjects was 35% less than that of adults. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*.

The safety and efficacy in pediatric patients other than those with asthma have not been established.

8.5 Geriatric Use

Clinical trials of NUCALA did not include sufficient numbers of subjects aged 65 years and older that received NUCALA (n = 46) to determine whether they respond differently from younger subjects. 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

Single doses of up to 1,500 mg have been administered intravenously to subjects in a clinical trial 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.

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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 SC 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 (2.3)]*. Each vial delivers mepolizumab 100 mg, 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 SC use. It is supplied in a single-dose, 1-mL, prefilled autoinjector with a fixed 29-gauge, half-inch needle or 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.

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 and EGPA. 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 and EGPA 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 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 SC, 125 mg SC, 250 mg SC, or 75 mg IV. Sixty-six of the 70 randomized subjects completed the trial. Compared with

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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. 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 SC, 75-mg IV, 125-mg SC, and 250-mg SC treatment groups, respectively. The model-predicted SC 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 subjects with asthma (Trial 1) supported the evaluation of mepolizumab 75 mg IV and 100 mg SC in the confirmatory asthma trials *[see Clinical Studies (14.1)]*. Following SC administration of mepolizumab 100 mg every 4 weeks for 32 weeks in subjects with 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. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

Following SC administration of mepolizumab 300 mg every 4 weeks for 52 weeks in subjects with EGPA, 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 (14.2)]*.

12.3 Pharmacokinetics

Following SC dosing in 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 EGPA were similar to the pharmacokinetic properties observed in subjects with severe asthma.

Systemic exposure following administration of mepolizumab 300 mg subcutaneously in subjects with EGPA was approximately 3 times that of mepolizumab 100 mg administered subcutaneously in subjects with severe asthma (Trial 2).

<u>Absorption</u>

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

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

<u>Distribution</u>

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

<u>Metabolism</u>

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

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Elimination

Following SC administration of mepolizumab in 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 subjects with asthma is estimated to be 0.28 L/day for a 70-kg individual.

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.

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 NUCALA. 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

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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 included 3 double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial (Trial 1, NCT #01000506) and 2 confirmatory trials (Trial 2, NCT #01691521 and Trial 3, NCT #01691508). Mepolizumab was administered every 4 weeks in all 3 trials as add-on to background treatment. All subjects 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 subjects with 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. Subjects 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 SC in the subsequent trials *[see Clinical Pharmacology (12.2)]*. NUCALA is not indicated for IV use and should only be administered by the SC route.

Confirmatory Trials

A total of 711 subjects with asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials subjects 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 subjects with 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. Subjects 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 subjects with asthma who required daily OCS in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control. Subjects in Trial 3 were not required to have a history of exacerbations in the previous year. Subjects 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.

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The demographics and baseline characteristics of these 3 trials are provided in Table 2.

Table 2. Demographics and Baseline Characteristics of Asthma Trials

	Trial 1 (N = 616)	**Trial 2 (N = 576)**	**Trial 3 (N = 135)**
Mean age (y)	49	50	50
Female, n (%)	387 (63)	328 (57)	74 (55)
White, n (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, mean (y)	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

The primary endpoint for Trials 1 and 2 was the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For subjects 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, subjects 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 3).

Table 3. Rate of Exacerbations in 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		

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	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).

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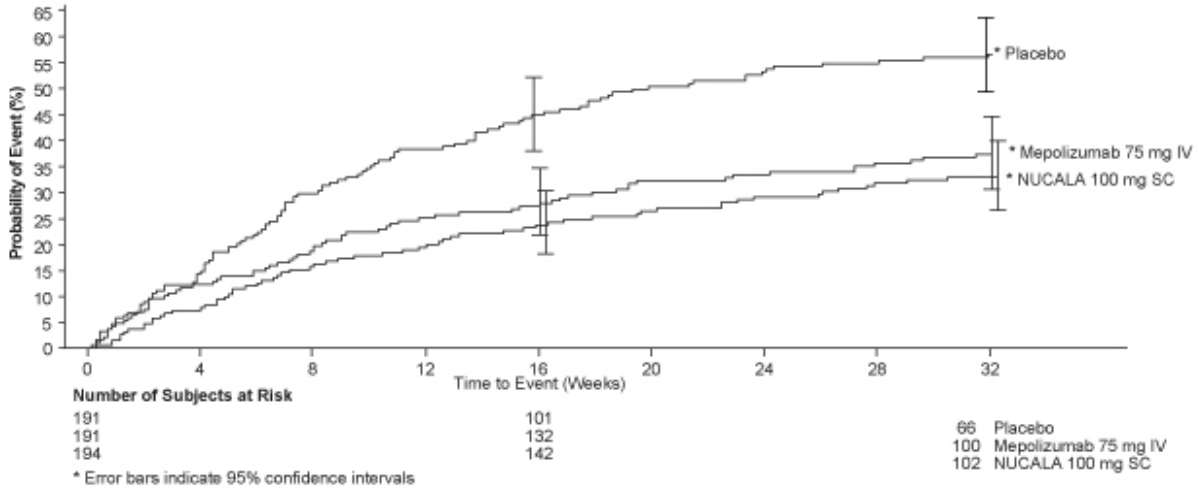
Figure 1. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Asthma Trial 2)



IV = intravenous, SC = subcutaneous.

Trial 1 data were explored to determine criteria that could identify subjects 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, subjects 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. The primary endpoint was the percent reduction of OCS dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Subjects were classified according to their

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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, subjects receiving NUCALA 100 mg achieved greater reductions in daily maintenance OCS dose, while maintaining asthma control. Sixteen (23%) subjects 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%) subjects 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 subjects receiving NUCALA 100 mg achieved at least a 50% reduction in the daily prednisone dose compared with 33% of subjects receiving placebo (95% CI for difference: 4%, 37%). An exploratory analysis was also performed on the subgroup of 29 subjects in Trial 3 who had an average baseline and screening blood eosinophil count <150 cells/mcL. Five (29%) subjects 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%) subjects 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 4. Compared with placebo, NUCALA 100 mg did not provide consistent improvements in mean change from baseline in FEV_1.

Table 4. Change from Baseline in FEV_1 (mL) in 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

[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.

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14.2 Eosinophilic Granulomatosis with Polyangiitis

A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT #02020889). Subjects 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. The co-primary endpoints were 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 subjects 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 subjects in this trial are provided in Table 5.

Table 5. Demographics and Baseline Characteristics in EGPA

	N = 136
Mean age (y)	48.5
Female, n (%)	80 (59)
White, n (%)	125 (92)
Duration (y) of EGPA, 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)

[a] Prednisone or prednisolone equivalent.
[b] e.g., Azathioprine, methotrexate, mycophenolic acid.
EGPA = eosinophilic granulomatosis with polyangiitis, SD = standard deviation.

Remission

Subjects receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of subjects receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (Table 6). Results of the components of remission are also shown in Table 6. In addition, significantly more subjects receiving 300 mg of NUCALA achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for 300 mg of NUCALA versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

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Table 6. 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 (mepolizumab/placebo)[a] (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of subjects at both Weeks 36 and 48						
Subjects, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (mepolizumab/placebo)[a] (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

[a] An odds ratio >1 favors mepolizumab.

EGPA = eosinophilic granulomatosis with polyangiitis, OCS = oral corticosteroid, BVAS = Birmingham Vasculitis Activity Score.

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 subjects receiving 300 mg of NUCALA compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 2). Additionally, subjects receiving 300 mg of NUCALA had a reduction in rate of relapse compared with subjects 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 mepolizumab compared with placebo.

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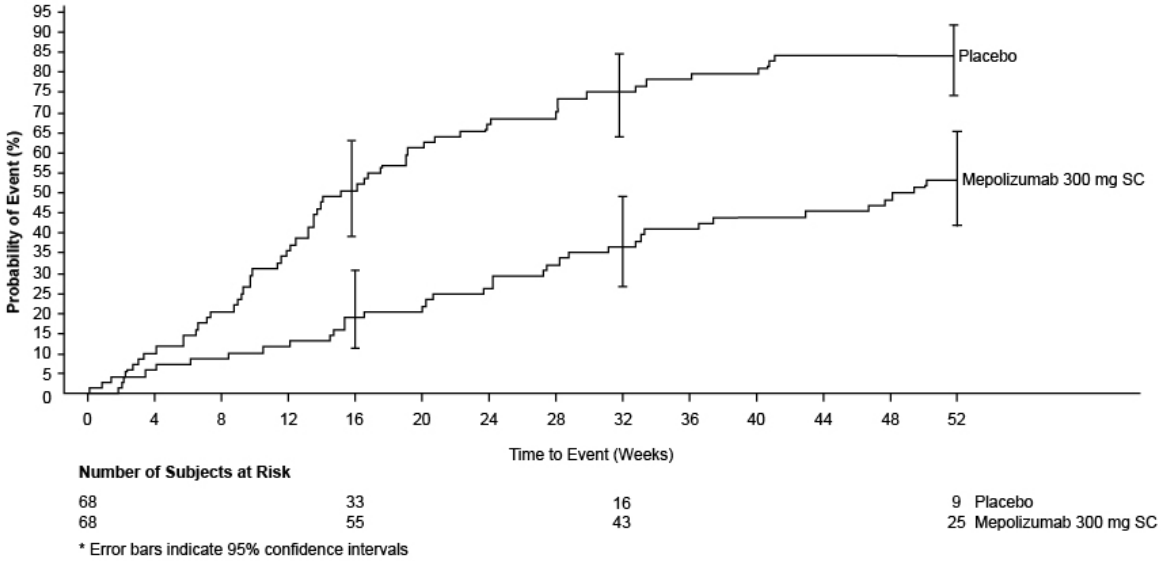
Figure 2. Kaplan-Meier Plot of Time to First Relapse in EGPA



EGPA = eosinophilic granulomatosis with polyangiitis, SC = subcutaneous.

Corticosteroid Reduction

Subjects receiving 300 mg of NUCALA had a significantly greater reduction in average daily OCS dose compared with subjects receiving placebo during Weeks 48 to 52 (Table 7).

Table 7. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of Subjects	
	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: mepolizumab/placebo[a]		
Odds ratio[b]		0.20
95% CI		0.09, 0.41

[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 mepolizumab.
EGPA = eosinophilic granulomatosis with polyangiitis.

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Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the subject, 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).

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 SC 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 SC use. Each single-dose prefilled autoinjector or single-dose prefilled syringe is designed to deliver 100 mg of mepolizumab in 1 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 in cartons of 1 (NDC 0173-0892-42).

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.

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17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

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.

Pregnancy Exposure Registry

Inform women there is a pregnancy exposure registry that monitors pregnancy outcomes in women with asthma exposed to NUCALA during pregnancy and that they can enroll in the Pregnancy Exposure Registry by calling 1-877-311-8972 or by visiting www.mothertobaby.org/asthma *[see Use in Specific Populations (8.1)]*.

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PHARMACIST—DETACH HERE AND GIVE PATIENT INFORMATION TO PATIENT

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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 used with other medicines:
  - for add-on maintenance treatment of asthma in people 12 years of age and older whose asthma is not controlled with their current asthma medicines. NUCALA helps prevent severe asthma attacks (exacerbations).
  - 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.
- Medicines such as NUCALA reduce blood eosinophils. Eosinophils are a type of white blood cells that may contribute to your disease.
- NUCALA is not used to treat sudden breathing problems that occur with asthma.

It is not known if NUCALA is safe and effective in children with severe asthma under 12 years of age.
It is not known if NUCALA is safe and effective in children and adolescents with EGPA under 18 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.
  - **Pregnancy Registry**. There is a pregnancy registry for women with asthma who receive NUCALA while pregnant. The purpose of the registry is to collect information about the health of you and your baby. You can talk to your healthcare provider about how to take part in this registry or you can get more information and register by calling 1-877-311-8972 or go to www.mothertobaby.org/asthma.
- 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.

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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:

- Use NUCALA every 4 weeks exactly as your healthcare provider tells you to.
- Read the Instructions for Use that comes with NUCALA for instructions about the right way to give your injections at home.
- NUCALA may be prescribed as a single-dose prefilled autoinjector or as a single-dose prefilled syringe.
- Before you use NUCALA, your healthcare provider will show you or your caregiver how to give the injections.
- You should inject NUCALA under your skin (subcutaneously) into your thigh or stomach (abdomen). Also, a caregiver may give the injection in your 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 weakness (fatigue). These are not all 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).

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- 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 needed, 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:xPIL

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: June 2019

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Instructions for Use

NUCALA
(mepolizumab)
injection, for subcutaneous use

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 needed, 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.

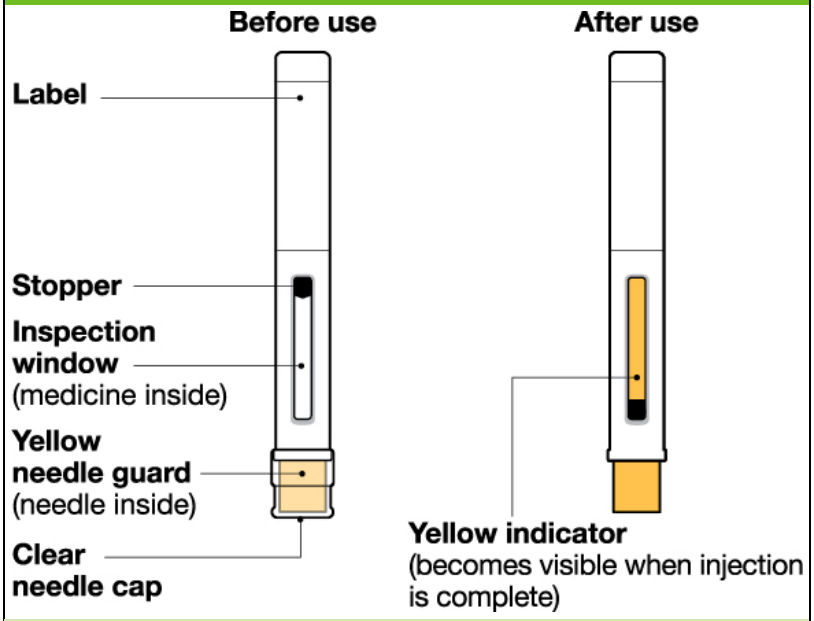
Keep NUCALA and all medicines out of the reach of children.

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.

Reference ID: 4444761

Know your prefilled autoinjector



Supplies in carton

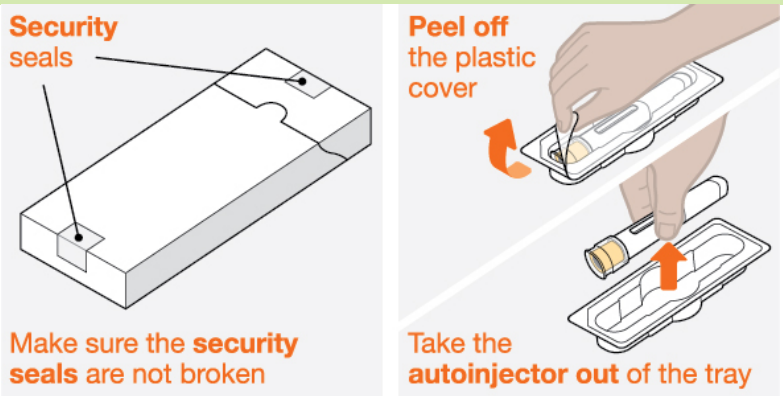
1 Prefilled autoinjector

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

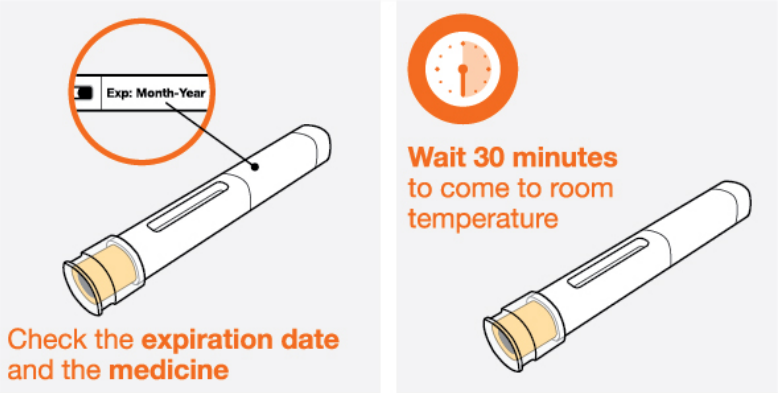
1. Take out the prefilled autoinjector



- 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.

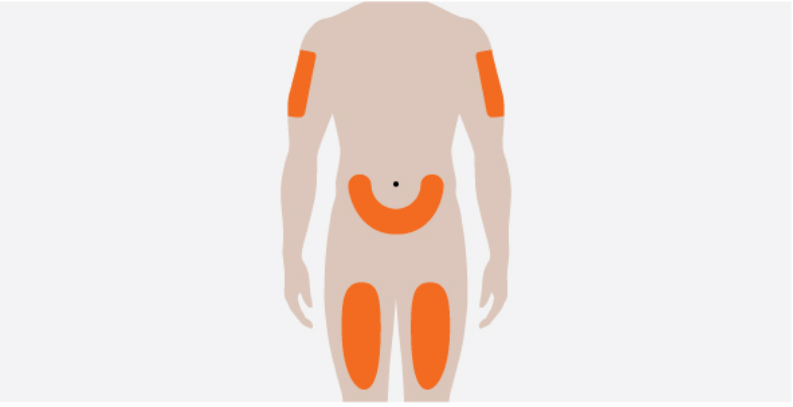
- Place the prefilled autoinjector on a clean, flat surface, away from direct sunlight and out of the reach of children.
  - **Do not** use the prefilled autoinjector if the security seal on the carton is broken. Contact GSK for more information at 1-888-825-5249.
  - **Do not** remove the clear needle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

2. Inspect and allow to come to room temperature



- 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 slightly yellow or pale brown in color and without cloudiness or particles.
- It is normal to see 1 or more air bubbles.
- For a more comfortable injection, allow the prefilled autoinjector to come to room temperature for up to 30 minutes 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.

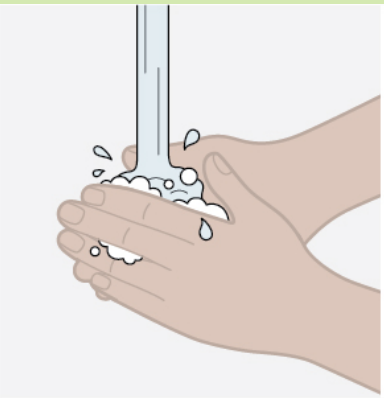
3. Choose your injection site



- 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.

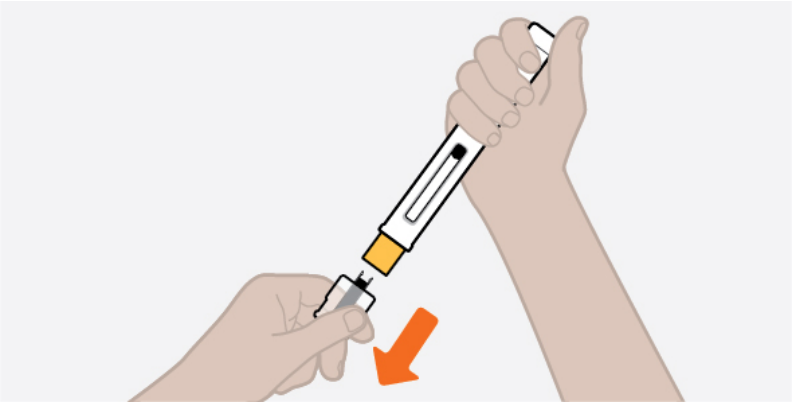
4. Clean your injection site



- 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.

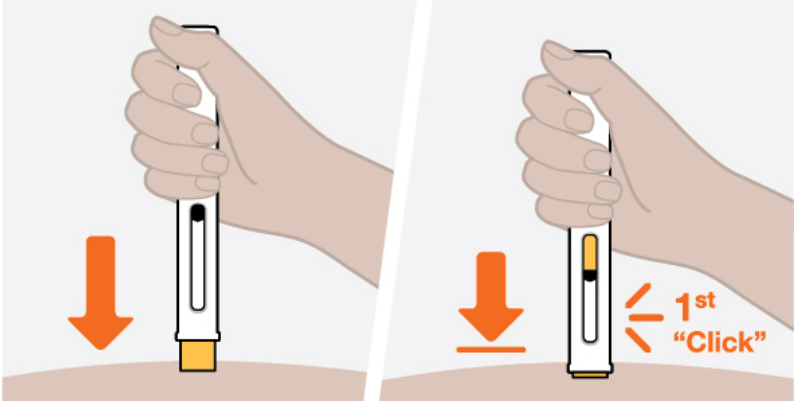
Inject

5. Remove the clear needle cap



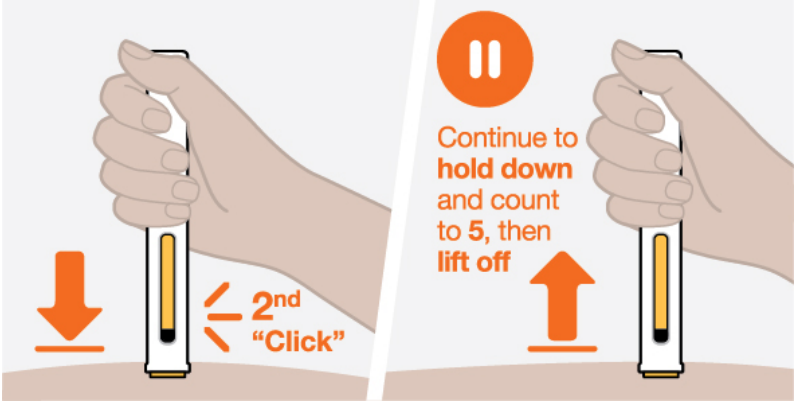
- Remove the clear needle cap from the prefilled autoinjector by pulling it straight off, away from the yellow needle guard (as shown). It may take some force to remove the clear needle cap.
- You may see a drop of medicine at the end of the needle. This is normal.
- Make sure you inject within 5 minutes 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

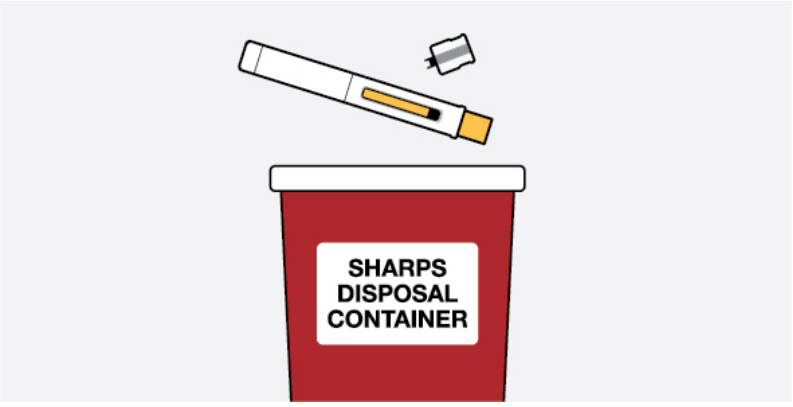


- Your injection may take up to 15 seconds to complete.
- Continue to hold the autoinjector down until you hear the 2nd click, the stopper has stopped moving, and the inspection window is filled with the yellow indicator.
- After you hear the 2nd click, continue to hold and count to 5 before you lift 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:

http://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:xIFU-A

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: June 2019

Reference ID: 4444761

Instructions for Use

NUCALA
(mepolizumab)
injection, for subcutaneous use

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.

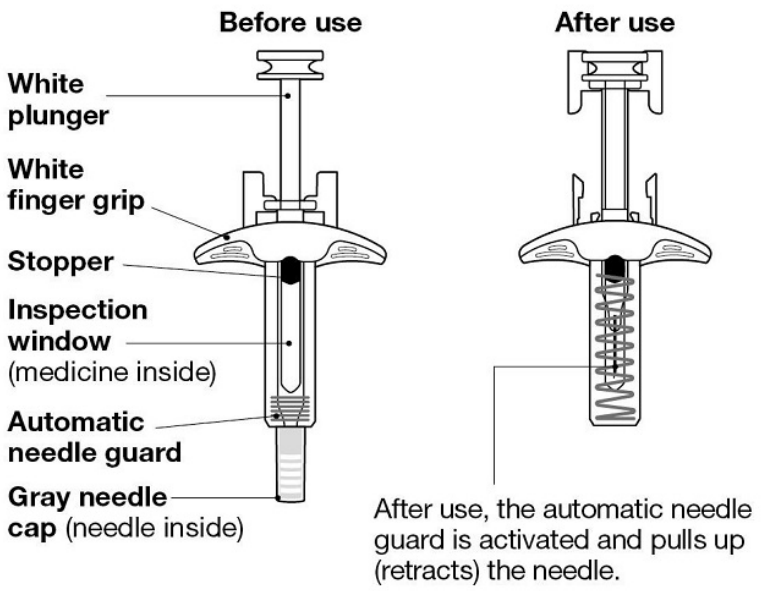
Keep NUCALA and all medicines out of the reach of children.

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.

Reference ID: 4444761

Know your prefilled syringe



Supplies in carton

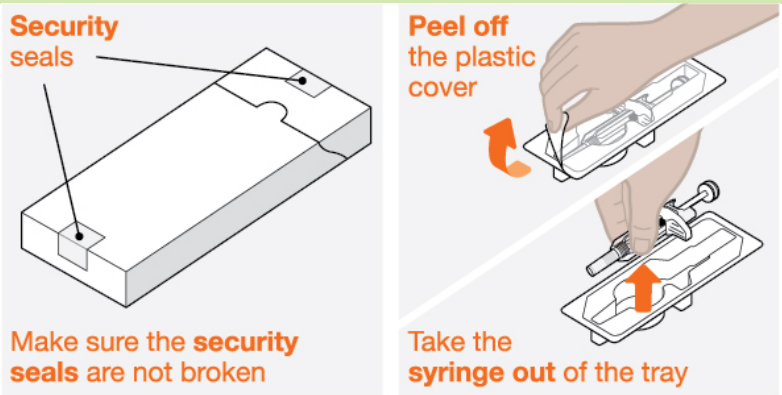
1 Prefilled syringe

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



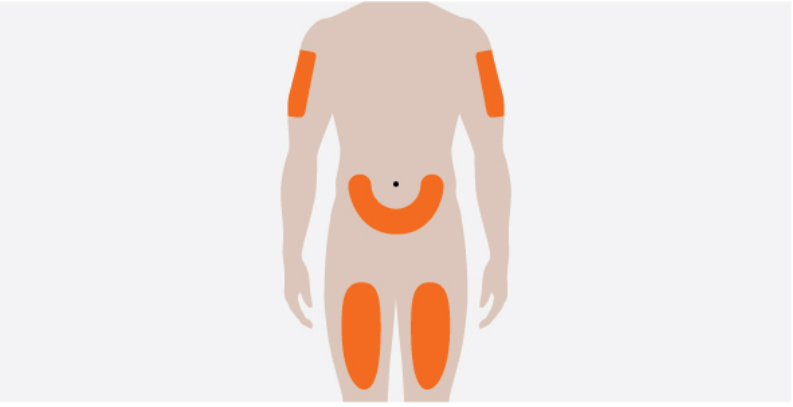
- Take the carton out of the refrigerator and make sure the security seals are not broken.
- Remove the tray from the carton.
- Peel off the clear plastic cover from the corner of the tray.
- Holding the middle of the prefilled syringe (near the inspection window), carefully take the prefilled syringe out of the tray.
- Place the prefilled syringe on a clean, flat surface, 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 allow to come to room temperature

- 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 slightly yellow or pale brown in color and without cloudiness or particles.
- It is normal to see 1 or more air bubbles.
- For a more comfortable injection, allow the prefilled syringe to come to room temperature for up to 30 minutes 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.

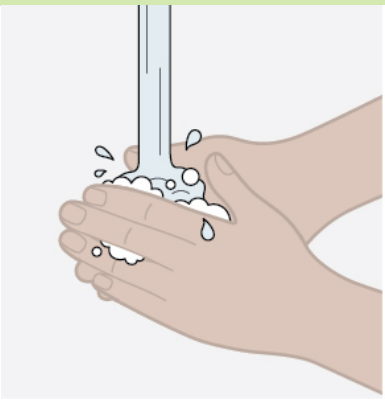
3. Choose your injection site

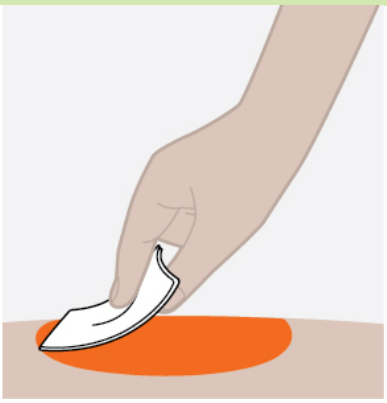


- You can inject in your thighs or abdomen.
- If you are giving the injection to someone else as a caregiver or healthcare provider, you can also inject into their upper arm.
- If you need more than 1 injection to complete your dose, leave at least 2 inches between each injection site.

- **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

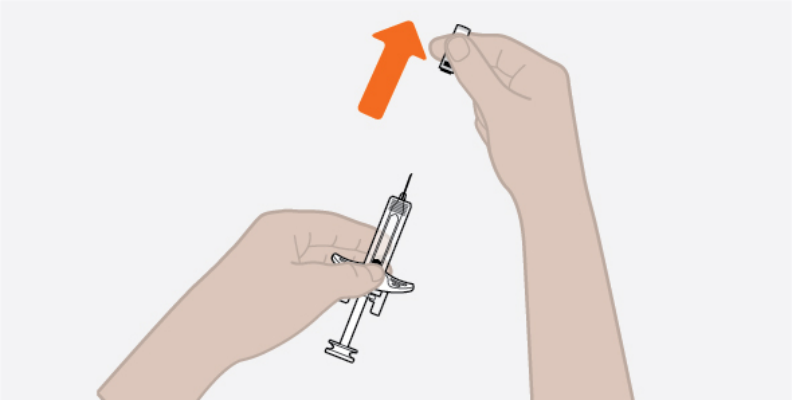




- Wash your hands with soap and water.
- Clean your injection site by wiping your skin with an alcohol swab and allowing your skin to air dry.
  - **Do not** touch your cleaned injection site again until you have finished your injection.

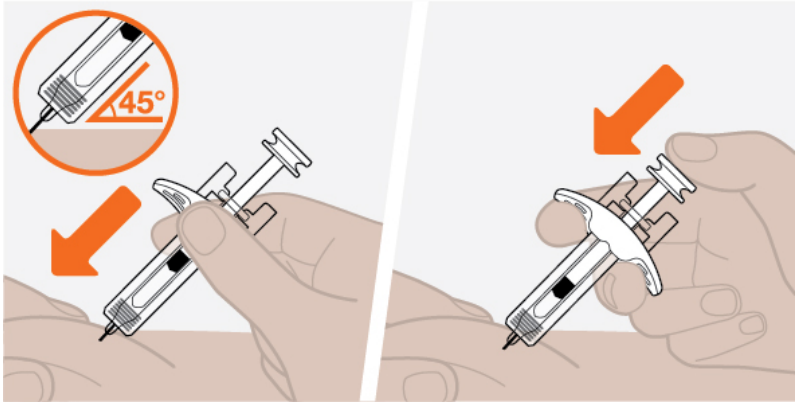
Inject

5. Remove the gray needle cap



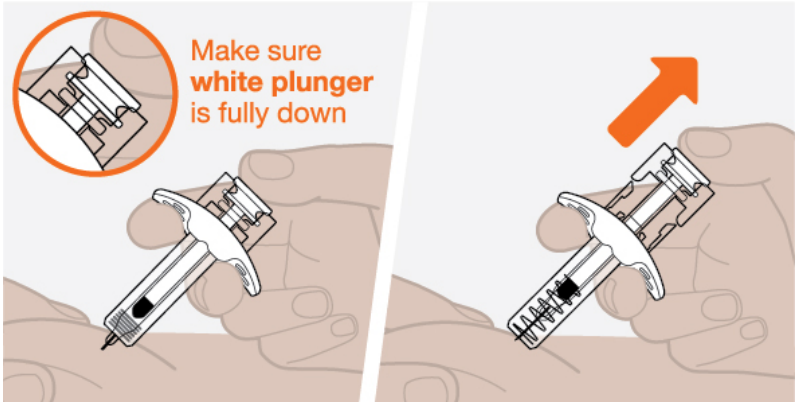
- Remove the gray needle cap from the prefilled syringe by pulling it straight off, away from the needle (as shown). It may take some force to remove the gray needle cap.
- You may see a drop of medicine at the end of the needle. This is normal.
- Make sure you inject within 5 minutes after you remove 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.

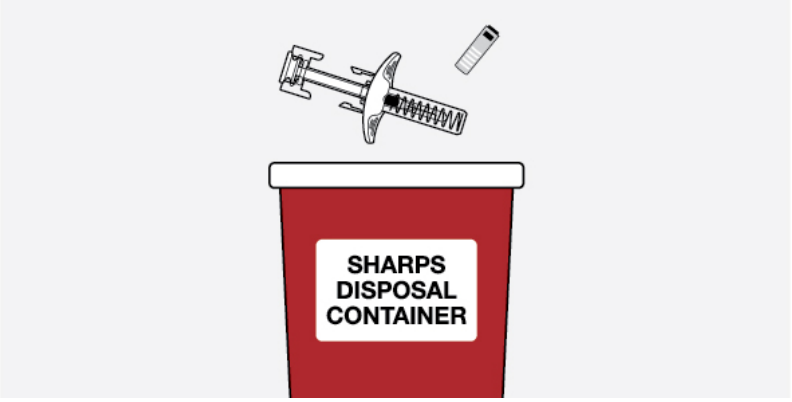
7. Complete your injection



- 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:

http://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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