

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrNUCALA

Mepolizumab for Injection

100 mg/mL lyophilized powder for subcutaneous injection

Interleukin-5 (IL-5) inhibitor

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
DESCRIPTION.....3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS4
WARNINGS AND PRECAUTIONS.....4
ADVERSE REACTIONS.....6
DRUG INTERACTIONS15
DOSAGE AND ADMINISTRATION15
OVERDOSAGE18
ACTION AND CLINICAL PHARMACOLOGY18
STORAGE AND STABILITY.....22
SPECIAL HANDLING INSTRUCTIONS22
DOSAGE FORMS, COMPOSITION AND PACKAGING22

PART II: SCIENTIFIC INFORMATION23
PHARMACEUTICAL INFORMATION.....23
CLINICAL TRIALS24
DETAILED PHARMACOLOGY33
TOXICOLOGY33
REFERENCES34

PART III: PATIENT MEDICATION INFORMATION35

PrNUCALA

Mepolizumab for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
By subcutaneous injection.	Lyophilized powder for subcutaneous injection. Each single-use vial contains 100 mg/mL mepolizumab after reconstitution.	No clinically relevant nonmedicinal ingredients. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

DESCRIPTION

NUCALA (mepolizumab for injection) is a humanised IgG1 kappa monoclonal antibody which binds with high affinity and specificity to soluble interleukin-5 (IL-5). Mepolizumab has a molecular weight of approximately 149 kDa and is produced by recombinant DNA technology in Chinese hamster ovary cells.

INDICATIONS AND CLINICAL USE

NUCALA (mepolizumab for injection) should be reconstituted and administered by a qualified healthcare professional who is experienced in the monitoring of signs and symptoms of hypersensitivity after administration of biologic agents and prepared to manage anaphylaxis that can be life-threatening (see WARNINGS and PRECAUTIONS, Hypersensitivity and Administration-Related Reactions and DOSAGE AND ADMINISTRATION).

Severe Eosinophilic Asthma

NUCALA (mepolizumab for injection) is indicated as add-on maintenance treatment of adult patients with severe eosinophilic asthma who:

- are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g. LABA), and

- have a blood eosinophil count of ≥ 150 cells/ μL (0.15 GI/L) at initiation of treatment with NUCALA OR ≥ 300 cells/ μL (0.3 GI/L) in the past 12 months.

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus (See WARNINGS AND PRECAUTIONS).

Eosinophilic Granulomatosis with Polyangiitis

NUCALA (mepolizumab for injection) is indicated as an add-on to corticosteroids for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Pediatrics (< 18 years of age):

NUCALA is not indicated in patients under 18 years of age.

Geriatrics (≥ 65 years of age):

There is limited safety and efficacy experience with NUCALA in patients over 65 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Patient Populations).

CONTRAINDICATIONS

NUCALA is contraindicated in patients who are hypersensitive to mepolizumab, to any ingredient(s) in the formulation, or component(s) of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

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 NUCALA. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days). These reactions may occur for the first time after a long duration of treatment.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma exacerbations.

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

Corticosteroid Reduction

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

Parasitic Infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical program. Patients with pre-existing helminth infections should be treated for their infection prior to therapy with NUCALA. If patients become infected whilst receiving treatment with NUCALA and do not respond to recommended anti-helminth treatment, temporary discontinuation of NUCALA should be considered.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, two serious adverse reactions of herpes zoster occurred in subjects treated with NUCALA compared with 1 in placebo (see ADVERSE REACTIONS). Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA.

Sexual Function/Reproduction

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

Effects on ability to drive and use machines

There have been no studies to investigate the effect of NUCALA on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology or adverse reaction profile of NUCALA.

Special Populations

Pregnant Women: No studies have been conducted with NUCALA in pregnant women (see TOXICOLOGY). In clinical trials there were too few pregnancies reported to inform on maternal and fetal health and development outcomes.

NUCALA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while receiving NUCALA and for up to 4 months after treatment is stopped.

Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women with severe eosinophilic asthma exposed to NUCALA, a pregnancy registry has been established. Healthcare professionals are encouraged

to register patients, and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting <http://mothertobaby.org/asthma>.

Nursing Women: There are no data regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production (see TOXICOLOGY).

A decision should be made whether to discontinue breast-feeding or discontinue NUCALA, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.

Pediatrics (< 18 years of age): NUCALA should not be used in patients under 18 years of age. There is limited clinical data in adolescents 12 to 17 years of age as only 28/1327 (2.1%) patients age 12 to 17 years old were enrolled in the severe asthma clinical trials with NUCALA and no patients age 12 to 17 were enrolled in the eosinophilic granulomatosis with polyangiitis clinical trial with NUCALA. The safety and efficacy of NUCALA has not been studied in children less than 12 years of age.

Geriatrics (≥ 65 years of age): There is limited safety and efficacy experience with NUCALA in patients over 65 years of age. A total of 119/1327 (9.0%) patients age 65 and older were enrolled in the severe asthma clinical trials with NUCALA and a total of 17/136 (13%) patients age 65 and older were enrolled in the eosinophilic granulomatosis with polyangiitis clinical trial with NUCALA. No dosage adjustment is required in patients 65 years or older (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Patient Populations).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In clinical studies in patients with severe eosinophilic asthma, the most commonly reported adverse drug reactions during treatment were headache, injection site reaction, and back pain. In patients with severe eosinophilic asthma, the safety profile was comparable between groups that received mepolizumab as a subcutaneous injection (NUCALA 100 mg) or intravenous infusion (75 mg, 250 mg and 750 mg).

In a clinical study in patients with eosinophilic granulomatosis with polyangiitis, the most commonly reported adverse drug reaction during treatment was headache.

Hypersensitivity reactions may occur within hours or days of being treated with NUCALA, including swelling of the face, mouth, and tongue; fainting, dizziness, or lightheadedness; hives; breathing problems and rash.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Severe Eosinophilic Asthma

The safety of mepolizumab has been studied in three randomized, placebo-controlled, multicentre clinical trials of 24 to 52 weeks duration and two open-label extension studies. A total of 1,327 patients with severe eosinophilic asthma received either a subcutaneous (SC) dose or an intravenous (IV) dose of mepolizumab or placebo during randomized controlled trials. Two of the three placebo-controlled studies included NUCALA 100 mg SC. Adverse events from these studies that were reported by 1% or more of patients with NUCALA 100 mg SC and that were reported more frequently than placebo ($\geq 1\%$ difference from placebo) are presented in [Table 1](#).

Table 1 On-treatment Adverse Events with $\geq 1\%$ incidence with NUCALA and $\geq 1\%$ more common with NUCALA than placebo in subjects with severe eosinophilic asthma

Adverse Events	NUCALA 100 mg SC (N = 263) n (%)	Placebo (N = 257) n (%)
Eye disorders		
Lacrimation increased	4 (1.5%)	0
Gastrointestinal disorders		
Gastroesophageal reflux disease	8 (3.0%)	3 (1.2%)
Dry mouth	4 (1.5%)	0
Gastrointestinal disorder	3 (1.1%)	0
General disorders and administration site conditions		
Injection site reaction ¹	21 (8.0%)	8 (3.1%)
Chest pain	5 (1.9%)	2 (0.8%)
Local swelling	3 (1.1%)	0
Infections and infestations		
Urinary tract infection	10 (3.8%)	5 (1.9%)
Pharyngitis	7 (2.7%)	4 (1.6%)
Injury, poisoning and procedural complications		
Ligament sprain	3 (1.1%)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (6.1%)	13 (5.1%)
Back pain	16 (6.1%)	9 (3.5%)
Muscle spasms	7 (2.7%)	1 (0.4%)
Musculoskeletal pain	4 (1.5%)	1 (0.4%)
Neck pain	4 (1.5%)	0
Musculoskeletal stiffness	3 (1.1%)	0
Tendonitis	3 (1.1%)	0
Nervous system disorders		
Headache	53 (20.2%)	47 (18.3%)
Psychiatric disorders		
Insomnia	7 (2.7%)	3 (1.2%)
Reproductive system and breast disorders		
Dysmenorrhoea	3 (1.1%)	0
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	7 (2.7%)	2 (0.8%)
Rhinorrhoea	5 (1.9%)	1 (0.4%)
Skin and subcutaneous tissue disorders		
Eczema	11 (4.2%)	2 (0.8%)

¹ The most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation.

Adverse drug reactions (events considered to be possibly related to treatment with mepolizumab) were identified following evaluation of all data from the three randomized placebo controlled trials and include headache (very common; $\geq 1/10$) and pharyngitis, lower respiratory tract

infection, urinary tract infection, nasal congestion, upper abdominal pain, eczema, back pain, pyrexia and injection site reactions (all common; $\geq 1/100$ to $< 1/10$).

Data summarized below are presented from the three completed placebo-controlled randomized clinical trials of 24 to 52 weeks duration in severe asthma for subjects receiving either mepolizumab (NUCALA 100 mg SC or mepolizumab 75, 250 or 750 mg IV) or placebo. Data are presented for both the NUCALA (100 mg SC) treatment group and for all subjects receiving any dose of mepolizumab (referred to as the ‘mepolizumab all doses combined’ treatment group).

Fatalities

In placebo-controlled studies, 5 subjects died: 3 subjects ($< 1\%$) receiving mepolizumab (severe acute pancreatitis and septic shock in 1 subject receiving 250 mg IV; asthma in 1 subject receiving 250 mg IV; asphyxia due to suicide in 1 subject receiving 750 mg IV) and 2 subjects ($< 1\%$) receiving placebo (road traffic accident; aspiration and gastrointestinal hemorrhage). None of the deaths were considered related to study medication by the investigator.

Serious Adverse Events

In placebo-controlled studies, serious adverse events were reported in 6% of subjects receiving NUCALA, 10% of subjects in the ‘mepolizumab all doses combined’ group and 15% of subjects receiving placebo. Serious adverse events of asthma occurred in 2% of subjects receiving NUCALA, 5% of subjects in the ‘mepolizumab all doses combined’ group and 9% of subjects receiving placebo.

Adverse Events leading to withdrawal from clinical trial

In placebo-controlled studies, 2% of subjects receiving NUCALA and 3% of subjects in the ‘mepolizumab all doses combined’ group withdrew due to an adverse event compared with 3% of subjects receiving placebo. The most frequent AE leading to withdrawal was asthma, which was reported by $< 1\%$ of subjects in both the ‘mepolizumab all doses combined’ and placebo groups; no subjects receiving NUCALA withdrew due to asthma. Adverse events leading to withdrawal in subjects receiving NUCALA included atrial flutter (1 subject), injection site reaction (1 subject) and urticaria (1 subject). An additional subject was withdrawn after receiving one dose of NUCALA due to a pre-existing medical condition of left bundle branch block. Adverse events leading to withdrawal in the ‘mepolizumab all doses combined’ group occurring in more than one subject included hypersensitivity (3 subjects: 1 received 250 mg IV and 2 received 750 mg IV) and arthralgia (2 subjects: 1 received 75 mg IV and 1 received 250 mg IV).

Immunogenicity

In clinical studies, overall, 15/260 (6%) of subjects treated with NUCALA developed anti-mepolizumab antibodies after having received at least one dose of NUCALA. Neutralizing antibodies were detected in one subject receiving NUCALA. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in

an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. The clinical impact of the presence of anti-mepolizumab antibodies is not known.

Adverse Events of Special Interest

Systemic Allergic Reactions: Systemic hypersensitivity reactions were reported by 1% of subjects receiving NUCALA, 1% of subjects in the ‘mepolizumab all doses combined’ group and 2% of subjects receiving placebo. All hypersensitivity reactions were reported as mild or moderate severity.

Infections: Overall infections were reported with similar frequency in the NUCALA (52%), ‘mepolizumab all doses combined’ (57%) and placebo (58%) treatment groups. Serious infections were reported by 3% of subjects in the NUCALA, ‘mepolizumab all doses combined’ and placebo treatment groups. The only serious infectious events that were reported in more than one subject in the ‘mepolizumab all doses combined’ group was pneumonia (4 subjects: 1 received NUCALA, 1 received 75 mg IV, 2 received 750 mg IV compared to 3 who received placebo); lobar pneumonia (2 subjects received 75 mg compared to 1 who received placebo) and herpes zoster (2 subjects received NUCALA compared to 0 in the placebo group). Opportunistic infections were infrequent and were reported in <1% of subjects in the placebo group and in 1% of subjects receiving NUCALA. One subject receiving NUCALA reported a helminth infection of parasitic gastroenteritis which resolved with treatment; NUCALA was continued.

Cardiovascular Events: Cardiac events were infrequent, occurring in 3% of placebo and ‘mepolizumab all doses combined’ patients and 2% of patients that received mepolizumab 100 mg SC/75 mg IV. Serious cardiac events occurred in <1% of subjects in the NUCALA, ‘mepolizumab all doses combined’ and placebo treatment groups.

Overall vascular events were reported with similar frequency in the NUCALA (3%), ‘mepolizumab all doses combined’ (5%) and placebo (6%) treatment groups. Serious vascular events were also infrequent and occurred in <1% in the ‘mepolizumab all doses combined’ group compared to 0% in both the NUCALA and placebo treatment groups.

Injection Site Reactions: Injection site reactions occurred more frequently in the NUCALA group (8%) compared with 3% in both the ‘mepolizumab all doses combined’ and placebo treatment groups. Symptoms included mild or moderate rash, itching, swelling, burning and pain at the injection site.

Neoplasms and Malignancies: Neoplasms were reported by 2% of subjects in the placebo group and <1% of subjects in both the NUCALA and the ‘mepolizumab all doses combined’ groups. Malignancies were reported by 3 subjects (<1%) in the placebo group and 2 subjects (<1%) in the ‘mepolizumab all doses combined’ group; no malignancies were reported in subjects receiving NUCALA. Malignancies reported during the studies included basal cell carcinoma, basosquamous carcinoma, prostate cancer, uterine cancer and squamous cell carcinoma.

Less Common Clinical Trial Adverse Events

In addition to the events shown in [Table 1](#), adverse events reported less commonly (defined as <1% in the ‘mepolizumab all doses combined’ treatment group) from the placebo-controlled severe asthma clinical trials and were reported in 2 or more patients receiving NUCALA compared to no reports in patients receiving placebo are summarized below.

Blood and lymphatic system disorders: iron deficiency anemia

Endocrine disorders: cushingoid

Eye disorders: lacrimation increased

Gastrointestinal disorder: dry mouth, gastrointestinal disorder

Injury, poisoning and procedural complications: administration related reaction, wrist fracture, stress fracture

Metabolism and nutrition disorders: diabetes mellitus, hypoglycemia, vitamin B12 deficiency

Musculoskeletal and connective tissue disorders: musculoskeletal stiffness

Renal and urinary disorders: pollakiuria

Skin and subcutaneous disorder: miliaria

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of NUCALA. Frequencies are included in brackets:

Immune System Disorders: Hypersensitivity reactions including anaphylaxis (*rare*)

Eosinophilic Granulomatosis with Polyangiitis

The safety of NUCALA has been studied in a double-blind, randomized, placebo-controlled, multicenter, 52-week treatment trial. A total of 136 subjects with EGPA were evaluated. Subjects received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Adverse events from this study that were reported by 5% or more of patients with NUCALA 300 mg SC and that were reported more frequently than placebo ($\geq 1\%$ difference from placebo) are presented in [Table 2](#).

Table 2 On-treatment Adverse Events with $\geq 5\%$ incidence with NUCALA and $\geq 1\%$ more common with NUCALA than placebo in subjects with EGPA

Adverse Events	NUCALA 300 mg SC (N =68) n (%)	Placebo (N = 68) n (%)
Ear and labyrinth disorders		
Vertigo	5 (7%)	1 (1%)
Eye disorders		
Vision blurred	4 (6%)	2 (3%)
Gastrointestinal disorders		
Diarrhea	12 (18%)	8 (12%)
Vomiting	11 (16%)	4 (6%)
General disorders and administration site conditions		
Injection site reaction ¹	9 (13%)	7 (10%)
Asthenia	5 (7%)	3 (4%)
Infections and infestations		
Sinusitis	14 (21%)	11 (16%)
Upper respiratory tract infection	14 (21%)	11 (16%)
Urinary tract infection	5 (7%)	4 (6%)
Acute sinusitis	6 (9%)	2 (3%)
Rhinitis	5 (7%)	3 (4%)
Fungal skin infection	4 (6%)	3 (4%)
Gastroenteritis	5 (7%)	2 (3%)
Oral herpes	4 (6%)	3 (4%)
Investigations		
Alanine aminotransferase increased	5 (7%)	0
Weight increased	4 (6%)	1 (1%)
Injury, poisoning and procedural complications		
Ligament sprain	4 (6%)	1 (1%)
Musculoskeletal and connective tissue disorders		
Arthralgia	15 (22%)	12 (18%)
Back pain	9 (13%)	6 (9%)
Neck pain	8 (12%)	2 (3%)
Musculoskeletal pain	6 (9%)	2 (3%)
Nervous system disorders		
Headache	22 (32%)	12 (18%)
Paraesthesia	4 (6%)	3 (4%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	8 (12%)	5 (7%)
Skin and subcutaneous tissue disorders		
Rash	9 (13%)	6 (9%)
Pruritus	6 (9%)	1 (1%)
Urticaria	4 (6%)	1 (1%)

¹ The most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation.

No additional adverse drug reactions (events considered to be possibly related to treatment with mepolizumab) were identified to those reported in the severe asthma trials.

Fatalities

In clinical studies in patients with EGPA, 2 subjects receiving NUCALA died (fatal cardiac arrest in both cases). One death occurred in an open-label long-term access program containing subjects that participated in the placebo-controlled trial. Neither death was considered related to study medication by the investigators.

Serious Adverse Events

Serious adverse events were reported in 18% of subjects receiving NUCALA and 26% of subjects receiving placebo.

Adverse Events leading to withdrawal from clinical trial

Two subjects (3%) receiving NUCALA and 1 (1%) subject receiving placebo withdrew due to an adverse event. Adverse events leading to withdrawal in subjects receiving NUCALA included cardiac arrest (1 subject) and hypersensitivity (1 subject). Adverse events leading to withdrawal in subjects receiving placebo included pneumonia (1 subject).

Immunogenicity

In subjects treated with NUCALA 1/68 (1%) developed anti-mepolizumab antibodies. No neutralizing antibodies were detected in any subjects with EGPA.

Adverse Events of Special Interest

Systemic Allergic Reactions: Systemic hypersensitivity reactions were reported by 4% of subjects receiving NUCALA and in 1% of subjects receiving placebo. One subject receiving NUCALA reported a hypersensitivity reaction that was serious and severe, but was not considered anaphylaxis. Symptoms associated with this reaction included malaise, hypertension, chills, pallor, cold extremities, warm sensation in trunk and neck, dyspnea, and stridor. Two of the four reported events of hypersensitivity occurred on the day of dosing.

Infections: Overall infections were reported with similar frequency in the NUCALA (84%) and placebo (78%) treatment groups. Serious infections were reported by 6% of subjects in the NUCALA treatment group and 15% of subjects in the placebo treatment group. Events considered to represent potential opportunistic infections were reported in 7% of subjects receiving NUCALA and in 3% of subjects in the placebo group.

Cardiovascular Events: Cardiac events were reported in 6% of subjects that received NUCALA and 9% subjects that received placebo. Serious cardiac events occurred in 1% of subjects in the NUCALA treatment group and 3% of subjects in the placebo treatment group.

Injection Site Reaction: Injection site reactions occurred at a rate of 15% in subjects treated with NUCALA compared with 13% in subjects treated with placebo. Common symptoms included erythema, bruising, pain, swelling, and warm to touch.

Neoplasms and Malignancies: Neoplasms were reported by 1% of subjects in the NUCALA group and 4% of subjects in the placebo group. No malignancies were reported in subjects receiving NUCALA and 2 subjects (3%) were reported in the placebo group.

Less Common Clinical Trial Adverse Events

In addition to the events shown in [Table 2](#), adverse events reported less commonly (defined as <5% in the ‘mepolizumab’ treatment group) from the placebo-controlled MEA115921 clinical trial and were reported in 2 or more patients receiving NUCALA compared to no reports in patients receiving placebo are summarized below.

Infections and infestations: candida infection, herpes simplex, pharyngitis, influenza like illness

Musculoskeletal and connective tissue disorders: bursitis

Gastrointestinal disorder: haemorrhoids

Respiratory, thoracic and mediastinal disorders: nasal polyps, pulmonary pain, rhinitis allergic

Skin and subcutaneous disorder: skin lesion, rash pruritic

Injury, poisoning and procedural complications: muscle strain, skin abrasion

Investigations: aspartate aminotransferase increased, gamma-glutamyltransferase increased

Eye disorders: eye pruritic, eye pain

Ear and labyrinth disorders: deafness, tinnitus

Vascular disorders: hot flush

Immune system disorders: food allergy

Blood and lymphatic disorders: anaemia

Endocrine disorders: adrenal insufficiency, steroid withdrawal syndrome

DRUG INTERACTIONS

No formal interaction studies have been performed with NUCALA.

Drug-Drug Interactions

Interactions with other drugs have not been formally studied.

Drug-Food Interactions

NUCALA is administered as a subcutaneous injection; therefore interactions with food are not applicable.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

General: NUCALA should be reconstituted and administered by a qualified healthcare professional who is experienced in the monitoring of signs and symptoms of hypersensitivity after administration of biologic agents and prepared to manage anaphylaxis that can be life-threatening (see WARNINGS AND PRECAUTIONS).

Following reconstitution, NUCALA should be used immediately upon withdrawal from the vial into a syringe. NUCALA should only be administered as a subcutaneous injection (e.g., upper arm, thigh, or abdomen) (see DOSAGE AND ADMINISTRATION, Administration).

Recommended Dose and Dosage Adjustment

Severe Eosinophilic Asthma: The recommended dose of NUCALA is 100 mg administered subcutaneously once every 4 weeks.

Eosinophilic Granulomatosis with Polyangiitis: The recommended dose of NUCALA is 300 mg administered subcutaneously once every 4 weeks.

Preparation of the 300 mg dose for treatment of Eosinophilic Granulomatosis with Polyangiitis requires the reconstitution of 3 separate 100 mg vials (see DOSAGE AND ADMINISTRATION, Administration).

Pediatrics (< 18 years of age)

NUCALA is not indicated in patients under 18 years of age.

Geriatrics (≥ 65 years of age)

No dosage adjustment is required for elderly patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Patient Populations).

Renal Impairment

Dosage adjustments in patients with renal impairment are unlikely to be required (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Patient Populations).

Hepatic Impairment

Dosage adjustments in patients with hepatic impairment are unlikely to be required (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Patient Populations).

Missed Dose

If a dose is missed or the patient is unable to attend an appointment for one of the injections, the missed dose should be administered as soon as possible.

Administration

Instructions for reconstitution: NUCALA does not contain a preservative, therefore, reconstitution should be carried out under aseptic conditions.

1. Reconstitute the NUCALA powder in the vial **with 1.2 mL of sterile Water for Injection**, preferably using a 2 to 3 mL syringe and a 21 gauge to 27 gauge needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab and may appear colourless to pale yellow or pale brown. Do not mix with other medications.
2. The stream of sterile Water for Injection should be directed vertically onto the centre of the lyophilized 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. Reconstitution is typically complete within 5 minutes after the sterile water has been added, but it may take additional time.

*Note: **Do not shake** the reconstituted solution during the procedure as this may lead to excessive foaming or precipitation.*

3. 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 1000 rpm for no longer than 5 minutes is acceptable.

4. Visually inspect the reconstituted NUCALA 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 or mild foaming are expected, however, and are acceptable. If particulate matter remains in the solution, or if the solution appears cloudy or milky, the solution must not be used.
5. If more than one vial is required for administration of the prescribed dosage, repeat steps 1 to 4.
6. If the reconstituted solution of NUCALA in the vial is not used immediately:
 - Store below 30°C.
 - Do not freeze.
 - Discard if not used within 8 hours of reconstitution.

Instructions for administration: 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.

1. Just prior to administration, remove 1 mL of reconstituted NUCALA. **Do not shake** the reconstituted NUCALA solution during the procedure as this could lead to product foaming or precipitation.
2. 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 be separated by at least 5 cm.

OVERDOSAGE

There is no clinical experience with overdose of NUCALA.

Single doses of up to 1500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

Treatment

There is no specific treatment for an overdose with NUCALA. 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

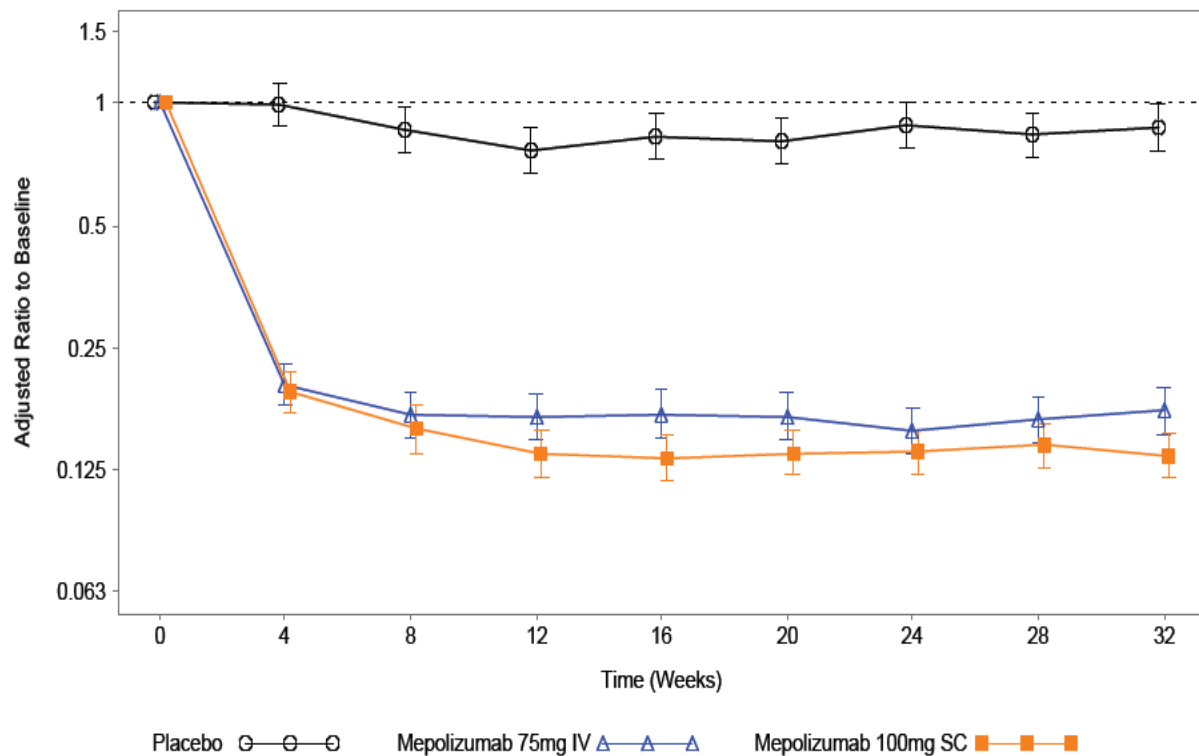
NUCALA is a targeted anti- interleukin-5 (IL-5) IgG1 kappa monoclonal antibody. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to soluble IL-5 with high affinity (a dissociation constant of 100 pM), preventing IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby reducing the production and survival of eosinophils. Inflammation is an important component in the pathogenesis of asthma and eosinophilic granulomatosis with polyangiitis. The reduction of eosinophilic inflammation may play an important role in eliciting a therapeutic effect in the treatment of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis; however, the precise mechanism of mepolizumab action has not been definitively established.

Pharmacodynamics

Severe Eosinophilic Asthma: Dose-dependent pharmacodynamic responses, i.e. reductions in blood eosinophil levels from baseline, were observed in asthma patients with mean baseline blood eosinophil levels greater than 300 cells/ μ L (ranged 150 – 2420 cells/ μ L) following treatment with mepolizumab. Subjects were assigned to receive one of four mepolizumab treatments (administered every 4 weeks for a total of three doses): 12.5 mg SC, 125 mg SC, 250 mg SC, or 75 mg IV. Sixty-six (66) of the 70 randomized subjects completed the trial. A reduction in blood eosinophil levels was observed in all treatment groups by Day 3. On Day 84 (4 weeks post-last dose), model-estimated inhibition of blood eosinophils was 57% (95% CI: 42, 69), 86% (95% CI: 83, 88), 86% (95% CI: 83, 89), and 88% (95% CI: 85, 90) in the 12.5 mg SC, 75 mg IV, 125 mg SC, and 250 mg SC treatment groups, respectively. The SC model-estimated doses to provide 50% and 90% of maximal inhibition of blood eosinophils at Day 84 were 11 and 99 mg, respectively.

Following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 32 weeks, blood eosinophils were reduced to a geometric mean count of 40 cells/ μ L, which corresponds to a geometric mean reduction of 84% compared with placebo. This magnitude of reduction was observed at the first post-dose measurement interval (4 weeks) and was maintained throughout the treatment period. Comparable results were observed following mepolizumab intravenous (IV) administration at 75 mg and SC administration at 100 mg ([Figure 1](#)).

Figure 1 Reduction in blood eosinophils from baseline over 32 weeks (MENSA)



Eosinophilic Granulomatosis with Polyangiitis: Following subcutaneous 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/ μ L. There was a geometric mean reduction of 83% compared to placebo and this magnitude of reduction was observed within 4 weeks of treatment (see CLINICAL TRIALS).

Pharmacokinetics

Following subcutaneous dosing in subjects with moderate/severe asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. In a population pharmacokinetic analysis, the pharmacokinetics of mepolizumab in subjects with EGPA dosed at 300 mg subcutaneously is consistent with that reported in subjects with 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.

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 250 mg 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, steady-state is reached by 16 weeks and there is approximately a two-fold accumulation at steady state.

Distribution: Following a single intravenous administration of mepolizumab to patients with asthma, the mean volume of distribution is 55 to 85 mL/kg.

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

Elimination: Following subcutaneous administration of mepolizumab, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In a population pharmacokinetic analysis, the estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special Patient Populations

Race or Gender

A population pharmacokinetics analysis of mepolizumab data indicated that there was no significant effect of race and gender on mepolizumab clearance.

Geriatrics (≥ 65 years old)

No formal studies have been conducted in elderly patients. However, in the population pharmacokinetic analysis, there were no indications of an effect of age (range included 12-82 years) on the pharmacokinetics of mepolizumab.

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, mepolizumab clearance was comparable between patients with creatinine clearance values between 50-80 mL/min and patients with normal renal function. There are limited data available in patients with creatinine clearance values <50 mL/min; however, mepolizumab is not cleared renally.

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.

STORAGE AND STABILITY

Unopened vial

Store in the original carton at room temperature (below 25°C) until use. Do not freeze. Protect from light.

Reconstituted solution

After reconstitution with Water for Injection, the product is stable for up to 8 hours when stored below 30°C. Do not freeze. During administration, protection from light is not necessary. Any unused concentrate or solution remaining after 8 hours must be discarded.

SPECIAL HANDLING INSTRUCTIONS

Do not mix the reconstituted NUCALA solution for injection with other medicinal products.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

NUCALA is a sterile, preservative-free, lyophilized powder for subcutaneous injection.

NUCALA is presented in a 10 mL type I glass vial with bromobutyl rubber (latex-free) stopper and a grey aluminum overseal with a plastic flip-cap.

NUCALA is available in a single-use vial for subcutaneous injection only.

Each single-use vial contains 144 mg of lyophilized mepolizumab. Upon reconstitution with 1.2 mL of sterile Water for Injection, USP, each vial delivers 100 mg mepolizumab in 1 mL, 160 mg/mL sucrose, 7.14 mg/mL sodium phosphate dibasic, heptahydrate, and 0.67 mg/mL polysorbate 80, with a pH of 7.0.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Mepolizumab
Chemical name:	Not applicable. Mepolizumab is not a chemical. It is an immunoglobulin (recombinant human IgG1 monoclonal antibody).
Molecular formula and molecular mass:	$C_{6476}H_{10084}N_{1732}O_{2028}S_{46}$ (without oligosaccharide) The polypeptide molecular mass is 146 kDa and the carbohydrate molecular mass is approximately 3 kDa resulting in a total estimated molecular mass of 149 kDa for mepolizumab.
Structural formula:	Mepolizumab is a humanized IgG1 kappa immunoglobulin and consists of two heavy chains of 449 amino acids and two light chains of 220 amino acids. The heavy and light chains are covalently linked by a single disulfide bond and the heavy chains are linked to each other by two disulfide bonds resulting in a typical IgG molecule.

Physicochemical properties: Mepolizumab is a clear to opalescent, colorless to pale yellow or pale brown solution.

Product Characteristics

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Mepolizumab is expressed as a soluble glycoprotein secreted into an animal component free cell culture medium, purified and formulated to produce bulk drug substance (BDS). NUCALA is a white lyophilized powder. After reconstitution with 1.2 mL of sterile Water for Injection, it forms a clear to opalescent, colorless to pale yellow or pale brown solution for subcutaneous injection. Upon reconstitution with sterile Water for Injection, each single-use vial delivers 100 mg mepolizumab in 1mL, 160 mg/mL sucrose, 7.14 mg/mL sodium phosphate dibasic, heptahydrate, and 0.67 mg/mL polysorbate 80, with a pH of 7.0.

CLINICAL TRIALS

Severe Eosinophilic Asthma

The efficacy and safety of adjunctive mepolizumab treatment in severe eosinophilic asthma was evaluated in 2 phase III, randomized, double-blind, parallel-group clinical trials of 24 to 32 weeks' duration in 711 subjects aged 12 years and older (Table 3):

- Exacerbation trial (MENSA) – 75 mg IV, 100 mg SC vs. placebo
- Oral corticosteroid (OCS) reduction trial (SIRIUS) – 100 mg SC vs. placebo

Both pivotal clinical trials were designed to evaluate the efficacy and safety of mepolizumab administered once every 4 weeks in subjects with severe eosinophilic asthma not adequately controlled on high-dose inhaled corticosteroid (ICS) (an equivalent of ≥ 1000 μg fluticasone propionate/day for subjects 18 years of age and older and an equivalent of ≥ 500 μg fluticasone propionate/day for subjects 12 to 17 years of age) and therapy with an additional controller(s). In SIRIUS, all subjects were required to be on regular maintenance treatment with OCS.

Table 3 Summary of trial design for MENSA and SIRIUS

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
MEA115588 (MENSA)	32-week, multicentre, randomised, double-blind, placebo-controlled, double-dummy, parallel-group study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma	NUCALA 100 mg SC Mepolizumab 75 mg IV ¹ Placebo Duration: 32 weeks	n=194 n=191 n=191 Total: 576	50 years (12-82)	Female: 329 (57%) Male: 247 (43%)
MEA115575 (SIRIUS)	24-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study of mepolizumab adjunctive therapy to reduce oral corticosteroid use in subjects with severe eosinophilic asthma	NUCALA 100 mg SC Placebo Duration: 24 weeks	n=69 n=66 Total: 135	50 years (16-74)	Female: 74 (55%) Male: 61 (45%)

IV = intravenous; SC = subcutaneous

¹NUCALA is not indicated for intravenous use and should only be administered by the SC route.

Mepolizumab as adjunctive therapy in patients with Severe Asthma (MENSA)

Study Design

MENSA was a 32-week, randomized, double-blind, parallel-group study evaluating the efficacy and safety of mepolizumab 75 mg IV and NUCALA 100 mg SC vs. placebo in the add-on treatment of severe eosinophilic asthma in 576 subjects (Table 3). MENSA was the only pivotal exacerbation study to evaluate the direct effect of the subcutaneous dosing on the exacerbation rate. The 100 mg SC and 75 mg IV doses were chosen to provide comparable systemic mepolizumab exposure and reduction of blood eosinophils over the treatment period (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics and Pharmacokinetics, Absorption).

Subjects had a history of two or more asthma exacerbations in the past 12 months despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (e.g. LABA, LTRA, or theophylline) with or without oral corticosteroids. Additionally, subjects had blood eosinophils of ≥ 150 cells/ μ L (≥ 0.15 GI/L) at initiation (within 6 weeks of first dose) or blood eosinophils of ≥ 300 cells/ μ L (≥ 0.3 GI/L) within 12 months of enrollment.

The primary endpoint was the frequency of clinically significant exacerbations of asthma, defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency room visits. For subjects on maintenance OCS, an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing maintenance dose for at least 3 days.

During the study, the percentage of patients who discontinued treatment and withdrew prematurely from the NUCALA 100 mg SC group, mepolizumab 75 mg IV group, and placebo group was 5%, 8% and 6%, respectively. The most common reason for discontinuation of treatment was patients withdrawing consent (3% overall).

Patient Demographics and Baseline Characteristics

Demographics and baseline characteristics were balanced between treatment groups (Table 4). During the trial, subjects continued their baseline asthma therapy (i.e. high-dose ICS with an additional controller(s)). Additionally, 24% of the subjects were on maintenance OCS (median 10.0 mg/day).

Table 4 Summary of patient demographics and baseline characteristics

	NUCALA 100 mg SC N=194	Mepolizumab 75 mg IV N=191	Placebo N=191
Mean age in years (range)	51 (12 - 81)	50 (13 - 82)	49 (12 - 76)
Gender, n (%)			
Male	78 (40)	85 (45)	84 (44)
Female	116 (60)	106 (55)	107 (56)
Mean duration of asthma in years (SD)	20.5 (12.9)	19.8 (14.0)	19.5 (14.6)
Mean % Predicted pre-bronchodilator FEV ₁ (SD)	59.3 (17.6)	61.4 (18.3)	62.4 (18.1)
Geometric mean baseline blood eosinophil count (SD on log scale) - GI/L	0.29 (1.050)	0.28 (0.987)	0.32 (0.938)
Mean number of exacerbations in the previous year (SD)	3.8 (2.7)	3.5 (2.2)	3.6 (2.8)

Study Results

The reduction in the rate of clinically significant exacerbations of asthma was statistically significant ($p < 0.001$) for both mepolizumab treatment groups compared with placebo (Table 5).

Compared with placebo, the reduction in the rate of exacerbations that required hospitalization or emergency room visits was statistically significant for NUCALA 100 mg SC, but not for mepolizumab 75 mg IV (Table 5). Additionally, the rate of clinically significant exacerbations requiring hospitalization per year in the NUCALA 100 mg SC, mepolizumab 75 mg IV, and placebo treatment groups were 0.03, 0.06 and 0.10, respectively.

Table 5 Summary of primary and secondary endpoints at Week 32¹

	NUCALA 100 mg SC N= 194	Mepolizumab 75 mg IV N = 191	Placebo N= 191
Frequency of Clinically Significant Exacerbations (Primary Endpoint)			
Exacerbation rate per year	0.83	0.93	1.74
Percent reduction vs. placebo	53%	47%	-
Rate ratio (95% CI)	0.47 (0.35, 0.64)	0.53 (0.40, 0.72)	
p-value ²	<0.001	<0.001	
Frequency of Clinically Significant Exacerbations Requiring Hospitalizations/Emergency Room Visits (Secondary Endpoint)			
Exacerbation rate per year	0.08	0.14	0.20
Percent reduction vs. placebo	61%	32%	-
Rate ratio (95% CI)	0.39 (0.18, 0.83)	0.68 (0.33, 1.41)	
p-value ²	0.015	0.299	

¹Analysis was performed using a negative binomial model which included covariates for treatment, use of maintenance oral corticosteroids, geographic region, number of exacerbations in the previous year, and baseline percentage of the predicted FEV₁.

²Type 1 error rate was controlled using a closed-testing procedure.

At Week 32, the mean change from baseline in pre-bronchodilator FEV₁ in the NUCALA 100 mg SC, mepolizumab 75 mg IV, and placebo treatment groups were 183 mL, 186 mL and 86 mL, respectively.

Health-related quality of life was measured using St. Georges Respiratory Questionnaire (SGRQ). At Week 32, mean changes from baseline in SGRQ scores in the NUCALA 100 mg SC, mepolizumab 75 mg IV, and placebo treatment groups were -16.0, -15.4 and -9.0, respectively.

SteroId ReductIon with mepolizUmab Study (SIRIUS)

Study Design

SIRIUS was a 24-week, randomized, placebo-controlled, double-blind, parallel group study that evaluated the effect of NUCALA 100 mg administered subcutaneously (SC) on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in patients with severe eosinophilic asthma. A total 135 subjects were enrolled in the study (Table 3).

Subjects were required to have blood eosinophils of ≥ 150 cells/ μ L at initiation (within 6 weeks of dosing) or blood eosinophils of ≥ 300 cells/ μ L within 12 months of enrollment. Similar to MENSA, subjects had a documented requirement for high-dose ICS with an additional controller(s) in the previous year. Additionally, all subjects were required to be on regular maintenance treatment with OCS (5 to 35 mg/day prednisone or equivalent). No exacerbation history was required; however the majority of patients (84%) had a history of at least one exacerbation in the previous year.

The study included a run-in optimization phase of 3-8 weeks, in which subjects' OCS dose was adjusted weekly, according to a pre-defined schedule, to establish the lowest dose of OCS required to maintain asthma control (hereafter referred to as baseline dose). Subjects were then randomized to receive either adjunctive NUCALA 100 mg SC or placebo treatment once every 4 weeks for 24 weeks. Reduction of the OCS dose occurred every 4 weeks (between Week 4 and Week 20) according to predefined schedule, and taking into account asthma control and adrenal insufficiency. The OCS dose was reduced until zero, or to the lowest possible dose required to maintain control during the 20 week OCS reduction phase. No further adjustment was made to the OCS dose following Week 20.

The primary endpoint was the percent reduction of OCS dose over Weeks 20 to 24 compared with the dose of OCS established during the run-in optimization phase at the start of the study. Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the OCS dose from the end of the optimisation phase.

During the study, the percentage of patients who discontinued treatment and withdrew prematurely from the NUCALA 100 mg SC group and placebo group was 4% and 6%, respectively. The most common reason for discontinuation of treatment was due to adverse events (5% placebo, 4% NUCALA 100 mg SC).

Patient Demographics and Baseline Characteristics

Demographics and baseline characteristics were balanced between treatment groups (Table 6). With the exception of OCS, subjects continued their baseline asthma therapy throughout the trial (i.e. high-dose ICS with an additional controller(s)).

Table 6 Summary of patient demographics and baseline characteristics

	NUCALA 100 mg SC N=69	Placebo N=66
Mean age in years (range)	50 (16 - 74)	50 (28 - 70)
Gender, n (%)		
Male	25 (36)	36 (55)
Female	44 (64)	30 (45)
Mean duration of asthma in years (SD)	17.4 (11.8)	20.1 (14.4)
Mean % Predicted pre-bronchodilator FEV ₁ (SD)	59.6 (17.0)	57.8 (18.5)
Geometric mean baseline blood eosinophil count (SD on log scale) - GI/L	0.25 (1.245)	0.23 (1.001)
Mean number of exacerbations in the previous year (SD)	3.3 (3.4)	2.9 (2.8)
Mean baseline daily OCS dose (mg)	12.4	13.2

Study Results

Subjects receiving NUCALA 100 mg SC achieved greater reductions in OCS dose compared to subjects receiving placebo, while maintaining asthma control (Table 7).

Table 7 Percent Reduction in OCS from Baseline at Weeks 20-24

	NUCALA 100 mg SC N= 69	Placebo N= 66
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
90% - 100%	16 (23%)	7(11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7(11%)
No decrease in OCS/lack of asthma control/withdrawal from treatment	25 (36%)	37 (56%)

For Weeks 20-24, 37 (54%) subjects in the NUCALA 100 mg SC group versus 22 (33%) subjects in the placebo group achieved $\geq 50\%$ reduction in the daily OCS dose; 37 (54%) subjects in the NUCALA 100 mg SC group versus 21 (32%) subjects in the placebo group achieved a reduction in the daily OCS dose to ≤ 5.0 mg; and 10 (14%) subjects in the NUCALA 100 mg SC group achieved a total (100%) reduction in OCS dose to 0 mg compared with 5 (8%) subjects in the placebo group.

Eosinophilic Granulomatosis with Polyangiitis

Study Design: The efficacy and safety of mepolizumab as an adjunct to oral corticosteroids for the treatment of patients with EGPA was evaluated in a phase III, multi-centre, randomized, double-blind, placebo-controlled study of 52 weeks duration in 136 subjects aged 18 years and older. Subjects received 300 mg of NUCALA or placebo administered subcutaneously once every 4 weeks, while maintaining stable oral corticosteroid therapy (Table 8). Starting at Week 4, oral corticosteroid dose could be tapered during the treatment period at the discretion of the investigator. The co-primary endpoints were: 1) the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus oral corticosteroid dose \leq 4 mg/day (prednisolone/prednisone); and 2) the proportion of subjects in remission at both Week 36 and Week 48 of treatment. Relapse of disease was defined as worsening or persistence of active disease since the last visit warranting: i) an increased dose of OCS therapy ($>$ 4 mg/day); OR ii) an increased dose or addition of immunosuppressive therapy; OR iii) hospitalization related to EGPA worsening. Worsening of active disease was characterized by: i) active vasculitis (BVAS $>$ 0); OR ii) active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR iii) active nasal and/or sinus disease with a corresponding worsening in at least one of the sino-nasal symptom questions.

Table 8 Summary of trial design for MEA115921

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender
MEA115921	52-week, multi-centre, randomised, double-blind, placebo-controlled study of mepolizumab in subjects with a history of relapsing or refractory EGPA on stable oral corticosteroid therapy with or without concomitant stable immunosuppressant therapy ^a .	NUCALA 300 mg SC Placebo Duration: 52 weeks	n=68 n=68 Total: 136	48.5 (20-71)	Female: 80 (59%) Male: 56 (41%)

SC = subcutaneous; EGPA = Eosinophilic Granulomatosis with Polyangiitis.

^a Excluding cyclophosphamide.

Patient Demographics and Baseline Characteristics: The demographics and baseline characteristics of subjects in this trial are provided in [Table 9](#).

Table 9 Summary of patient demographics and baseline characteristics

	NUCALA 300 mg SC N=68	Placebo N=68
Mean age (y)	48.7	48.2
Female, n (%)	42 (62)	38 (56)
White, n (%)	64 (94)	61 (90)
Duration (y) of EGPA, mean (SD)	5.24 (4.398)	5.85 (4.855)
History of ≥ 1 confirmed relapse in past 2 years, n (%)	51 (75)	49 (72)
History/presence of Asthma plus Eosinophilia ($>1.0 \times 10^9/L$), n (%)	68 (100)	68 (100)
Sino-nasal abnormality	64 (94)	64 (94)
Pulmonary infiltrates, non-fixed	50 (74)	48 (71)
Biopsy evidence ¹	25 (37)	31 (46)
Neuropathy, Mono or Poly ²	32 (47)	24 (35)
ANCA positive (MPO or PR3)	13 (19)	13 (19)
Cardiomyopathy ³	13 (19)	7 (10)
Palpable purpura	9 (13)	8 (12)
Alveolar hemorrhage ⁴	3 (4)	1 (1)
Glomerulonephritis ⁵	1 (1)	0
Refractory disease, n (%)	34 (50)	40 (59)
Recurrence of EGPA symptoms, n (%)	33 (49)	35 (51)
Failed induction treatment, n (%)	1 (1)	5 (7)
Baseline BVAS, median (range)	1 (0-22)	2 (0-19)
Baseline oral corticosteroid^a daily dose (mg), median (range)	12 (7.5-40)	11 (7.5-50.0)
Receiving immunosuppressive therapy, n (%)	41 (60)	31 (46)
Baseline ACQ-6 Score Category^{6,7}, n (%)		
≤ 0.75	23 (34)	19 (28)
>0.75 to <1.5	19 (28)	21 (31)
≥ 1.5	26 (38)	28 (41)

¹ A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation

² Motor deficit or nerve conduction abnormality

³ Established by echocardiography or MRI

⁴ Determined by bronchoalveolar lavage

⁵ Hematuria, red blood cell casts, proteinuria

⁶ ACQ-6 score ≤ 0.75 = well controlled asthma, >0.75 to <1.5 = some lack of asthma control, ≥ 1.5 = not well controlled asthma.

⁷ Summarized *post-hoc*.

^a Prednisone or prednisolone equivalent.

^b Excluding cyclophosphamide.

ANCA = anti-neutrophil cytoplasmic antibodies; EGPA = eosinophilic granulomatosis with polyangiitis; SD = standard deviation;

MPO = myeloperoxidase (ANCA-MPO); PR3 = proteinase 3 (ANCA-PR3).

Study Results

Remission

Subjects receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo (odds ratio: 5.9 [95% CI: 2.7, 13.0]; $p < 0.001$). Additionally, a significantly larger proportion of subjects receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (odds ratio: 16.7 [95% CI: 3.6, 77.7]; $p < 0.001$) (Table 10).

Table 10 Analyses of Co-Primary Endpoints

	Number (%) of Subjects	
	NUCALA 300 mg n = 68	Placebo n = 68
Accrued duration of remission over 52 weeks		
0 weeks	32 (47)	55 (81)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	9 (13)	3 (4)
24 to <36 weeks	10 (15)	0
≥36 weeks	9 (13)	2 (3)
Odds ratio (mepolizumab/placebo) ^a	5.91 ^b	
95% CI	2.68, 13.03	
P value	<0.001	
Proportion of subjects in remission at Weeks 36 and 48		
Subjects in remission at Weeks 36 and 48 (%)	22 (32)	2 (3)
Odds ratio (mepolizumab/placebo) ^a	16.74	
95% CI	3.61, 77.56	
P value	<0.001	

^aAn odds ratio >1 favors mepolizumab.

^b Obtained using a proportional odds regression model for ordered categorical data (incremental 12-week durations).

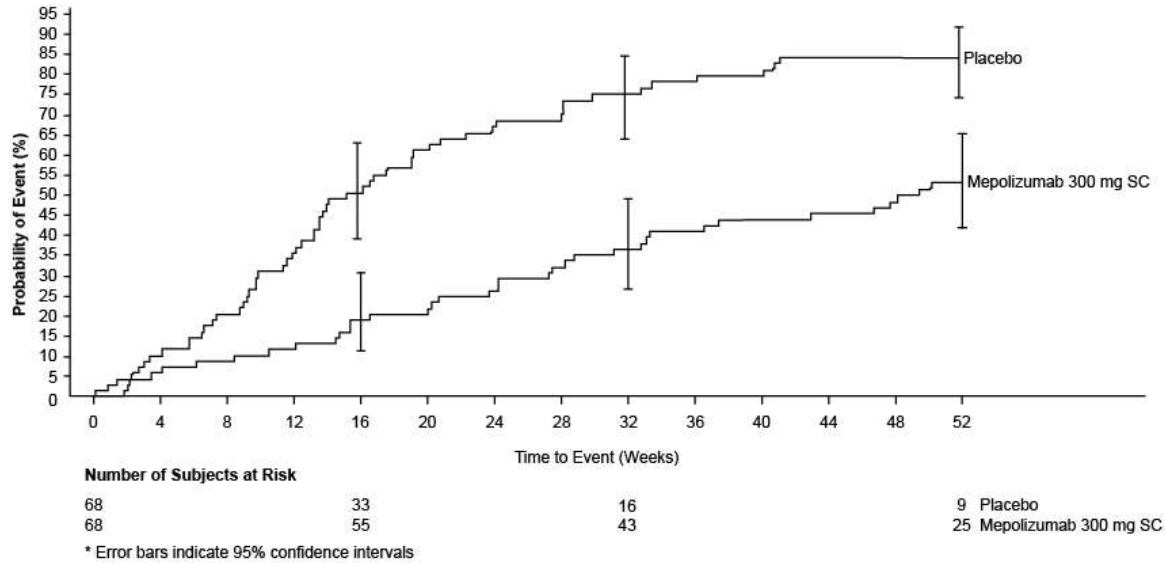
Statistically significant differences in favour of mepolizumab for these endpoints were also demonstrated by the European League Against Rheumatism (EULAR) definition of remission (i.e., BVAS = 0 plus oral corticosteroid dose ≤7.5 mg/day (prednisolone/prednisone)).

A larger proportion of subjects receiving 300 mg of NUCALA (n=13; 19%) achieved remission within the first 24 weeks of treatment and remained in remission for the remainder of the 52-week treatment period compared with placebo (n=1; 1%).

Relapse

The time to first relapse was significantly longer for subjects receiving 300 mg of NUCALA compared with placebo (hazard ratio: 0.32 [95% CI: 0.21, 0.50]; $p < 0.001$) (Figure 2). The incidence and number of each potential cause for relapse (i.e., vasculitis, asthma, sino-nasal) were lower in subjects treated with mepolizumab compared with placebo.

Figure 2 Kaplan-Meier Plot of Time to First Relapse



Oral Corticosteroid Reduction

Subjects receiving 300 mg of NUCALA had a significantly greater reduction in average daily oral corticosteroid dose compared with subjects receiving placebo during Weeks 48 to 52 (odds ratio: 0.20 [95% CI 0.09, 0.41]; $p < 0.001$) (Table 11).

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

Average Daily Oral Corticosteroid Dose	Number (%) of Subjects	
	NUCALA 300 mg Subcutaneous n = 68	Placebo n = 68
0	12 (18)	2 (3)
>0 to ≤4.0 mg	18 (26)	3 (4)
>4.0 to ≤7.5 mg	10 (15)	18 (26)
>7.5 mg	28 (41)	45 (66)
Comparison: mepolizumab/placebo ^a		
Odds ratio	0.20	
95% CI	0.09, 0.41	
P value	<0.001	

^a Analyzed using a proportional odds model with covariates of treatment group, baseline oral corticosteroid daily dose, baseline BVAS, and region. An odds ratio <1 favors mepolizumab.

DETAILED PHARMACOLOGY

Please refer to ACTIONS AND CLINICAL PHARMACOLOGY.

TOXICOLOGY

Intravenous and subcutaneous administrations to monkeys were associated with reductions in peripheral and lung eosinophil counts, with no toxicological findings. Eosinophils have been 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.

Carcinogenesis, Mutagenesis and Impairment of Fertility and Reproduction

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. The mutagenic potential of mepolizumab was not evaluated. The role of IL-5 and eosinophils in tumor surveillance is poorly characterized. However, there is no evidence of defective tumor surveillance in IL-5-deficient or eosinophil-deficient mice.

There was no effect of anti-IL-5 antibodies on male and female mice on mating, fertility, and gonadal function or on early embryonic or embryofetal development in pregnant females. Studies in mice did not include a littering or functional F1 assessment. In cynomolgus 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 monkeys demonstrate that mepolizumab crosses the placenta. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants. Mepolizumab was excreted into the milk of cynomolgus monkeys at concentrations that were less than 0.5% of those detected in plasma and there were no post-natal developmental effects in breastfed monkey offspring.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrNUCALA
[new-ka' la]

Mepolizumab for Injection

Read this carefully before you start taking NUCALA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NUCALA.

What is NUCALA used for?

Severe Eosinophilic Asthma

NUCALA (mepolizumab) is a prescription medicine used in addition to other asthma medicines to treat adult patients with severe eosinophilic asthma, whose asthma is not controlled with their current asthma medicines, such as high-dose inhalers. Severe eosinophilic asthma is a type of severe asthma in which there is a presence of eosinophils (a type of white blood cell). Eosinophils are associated with inflammation of the airways that can cause your asthma to get worse or can increase the number of asthma attacks. NUCALA helps prevent the number of asthma attacks.

NUCALA is not used to treat acute asthma symptoms, such as a sudden asthma attack.

Eosinophilic Granulomatosis and Polyangiitis (EGPA)

EGPA is a condition where people have inflammation of the blood vessels (vasculitis) due to too many eosinophils (a type of white blood cell) in the blood and tissues. EGPA most commonly affects the lungs and sinuses but often also affects other organs including the skin, heart, kidneys, nerves or bowels. The most common symptoms include extreme fatigue, muscle and joint pain, weight loss, sinonasal symptoms, and breathlessness.

NUCALA, used in addition to corticosteroids, can reduce EGPA symptoms and delay flare-up of these symptoms. NUCALA can also help reduce the daily dose of corticosteroids you need to control your symptoms.

How does NUCALA work?

NUCALA contains the active substance, mepolizumab, a monoclonal antibody that works by blocking a specific protein called interleukin-5. By blocking the action of interleukin-5, NUCALA limits the production of more eosinophils from the bone marrow and lowers the number of eosinophils in the blood, lungs and tissues.

What are the ingredients in NUCALA?

Medicinal ingredients: The active substance is mepolizumab.

Non-medicinal ingredients: The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, and polysorbate 80.

NUCALA comes in the following dosage form:

Lyophilized powder for subcutaneous injection; each single-use vial contains 144 mg of mepolizumab (100 mg/mL when reconstituted).

Do not use NUCALA if:

- you are **allergic** to mepolizumab or any of the other ingredients of this medicine. **Talk to your doctor** about whether this may apply to you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use NUCALA.

- Medicines of this type (monoclonal antibodies) can cause severe allergic reactions when injected into the body (see **What are the possible side effects from using NUCALA?**). If you have had a similar reaction before, tell your doctor before you are given NUCALA.
- NUCALA does not treat acute asthma symptoms, such as a sudden asthma attack. Therefore NUCALA should not be used to treat such symptoms.
- Tell your doctor if your asthma symptoms remain uncontrolled or get worse while being treated with NUCALA.
- Tell your doctor if you are taking corticosteroids or other medicines for the treatment of asthma or Eosinophilic Granulomatosis with Polyangiitis. **Do not suddenly stop taking** your corticosteroids or other medicines once you have started NUCALA. Corticosteroids must be stopped gradually, under the supervision of your doctor.

Talk about any health conditions or problems you may have, including:

- If you have an existing parasitic infection, live in a region where infections caused by parasites are common, or if you are travelling to such a region. NUCALA may weaken your resistance to such infections. Parasitic infections should be treated prior to starting treatment with NUCALA.
- If you have not had chickenpox (varicella) or chickenpox vaccine.

Pregnancy and breast-feeding:

- If you are pregnant, think you may be pregnant, or are planning to become pregnant, **tell your doctor** before using this medicine. You should not use this medicine if you are pregnant, unless this is considered necessary by your doctor. There is a pregnancy registry for women 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 <http://mothertobaby.org/asthma/>.
- If you become pregnant while being treated with NUCALA or within 4 months of stopping treatment with NUCALA, tell your doctor immediately.
- It is not known whether the ingredients of NUCALA can pass into breast milk. **If you are breastfeeding or plan to breastfeed, you must tell your doctor** before being treated with NUCALA.

Other warnings you should know about:

NUCALA should not be given to children and adolescents under 18 years old.

Tell your healthcare professional about all the medicines you take or have recently taken, including drugs, or medicines obtained without a prescription (vitamins, minerals, natural supplements or alternative medicines).

How to take NUCALA:

NUCALA is given to you as an injection just under the skin (subcutaneously) by a healthcare professional, who is experienced in the monitoring and treatment of signs and symptoms of allergic reactions.

Usual dose:

Severe Eosinophilic Asthma

The recommended dose of NUCALA for severe eosinophilic asthma is 100 mg, given as 1 injection under the skin (subcutaneous) every four weeks.

Eosinophilic Granulomatosis with Polyangiitis

The recommended dose of NUCALA for EGPA is 300 mg, given as 3 injections under the skin (subcutaneous) every four weeks.

Do not stop receiving injections of NUCALA unless advised by your doctor. Interrupting or stopping the treatment with NUCALA may cause your symptoms to become worse or occur more frequently. If your symptoms get worse when being treated with NUCALA, immediately tell your doctor.

Overdose:

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose of NUCALA is missed, contact your healthcare professional, such as doctor or nurse, as soon as possible to re-schedule your appointment.

What are possible side effects from using NUCALA?

Like all medicines, NUCALA 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.

These are not all the possible side effects that you may feel when taking NUCALA. If you experience any side effects not listed here, contact your healthcare professional.

Allergic or Allergic-like reactions

Some people may have allergic or allergic-like reactions. These reactions often occur within minutes to hours after the injection, but sometimes symptoms can start several days later. You may experience this type of reaction even if it is not your first injection of NUCALA.

Symptoms can include:

- becoming very wheezy, cough, difficulty breathing, chest tightness
- fainting, dizziness, suddenly feeling weak or lightheaded (due to a drop in blood pressure)
- swelling of your eyelids, face, lips, tongue, mouth, and other areas of the body (angioedema) skin rash, hives, redness

Stop taking NUCALA and seek medical attention immediately if you think you may be having a reaction.

If you may have had a similar reaction before (see also **To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUCALA**), **tell your doctor before you are given NUCALA.**

Very common side effects (may affect more than 1 in 10 people):

- Headache
- Joint Pain
- Sinus Infection
- Cough, sore throat, runny nose, nasal congestion (Upper respiratory tract infection)
- Diarrhea
- Vomiting
- Back pain
- Rash
- Neck pain

- Mouth and/or throat pain
- Injection site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)

Common side effects (may affect up to 1 in 10 people):

- Sore throat (pharyngitis)
- Congestion, cough, discomfort, fever (lower respiratory tract infection)
- Stuffy nose (nasal congestion)
- Stomach pain or discomfort in the upper area of the stomach (upper abdominal pain)
- Itchy red patches on the skin (eczema)
- Urinary tract infection (blood in urination, painful and frequent urination, fever, pain in lower back)
- High temperature (fever)
- Muscle and/or bone pain
- Sensation of spinning or feeling off balance, dizziness (Vertigo)
- Lack of energy, muscle weakness
- Sensation of tingling and/or numbness (Paraesthesia)
- Blurry vision

Tell your healthcare professional immediately if you get any of these symptoms, or if you notice any side effects not listed in this leaflet.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Sudden, severe allergic reaction: -skin rash (hives) or redness -swelling, sometimes of the face or mouth (angioedema) -becoming very wheezy, coughing or having difficulty breathing -suddenly feeling weak or light headed (may lead to collapse or loss of consciousness)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of the sight and reach of children.
- Do not use this medicine after the expiry date that is stated on the label.
- The expiry date refers to the last day of the stated month.
- Store in the original package to protect from light.
- Store at room temperature (below 25°C). Discard unused drug if reconstituted more than 8 hours.
- Do not shake or freeze.

If you want more information about NUCALA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.gsk.ca; or, by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

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