NUCALA

Mepolizumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lyophilised white powder.

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

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), directed against human interleukin-5 (IL-5) produced in Chinese hamster ovary cells by recombinant DNA technology.

CLINICAL INFORMATION

Indications

NUCALA is indicated as add-on maintenance treatment of severe eosinophilic asthma in patients 12 years and older (see *Clinical Studies*).

Dosage and Administration

Pharmaceutical form: Powder for solution for infusion.

NUCALA should be administered by a health care professional.

NUCALA should be prescribed by physcians experienced in the diagnosis and treatment of severe eosinophilic asthma.

Following reconstitution, *NUCALA* should only be administered as a subcutaneous injection (e.g. upper arm, thigh, or abdomen) (see *Use and Handling*).

Populations

Adults and Adolescents (12 years and older)

The recommended dose is 100 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children (up to 12 years of age)

The safety and efficacy of *NUCALA* have not been established in children less than 12 years of age.

Elderly (65 years or older)

No dosage adjustment is recommended in patients 65 years or older (see *Pharmacokinetics – Special Patient Populations*).

Renal Impairment

Dose adjustments in patients with renal impairment are unlikely to be required (see *Pharmacokinetics – Special Patient Populations*).

Hepatic Impairment

Dose adjustments in patients with hepatic impairment are unlikely to be required (see *Pharmacokinetics – Special Patient Populations*).

Contraindications

Hypersensitivity to mepolizumab or to any of the excipients.

Warnings and Precautions

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*.

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.

Hypersensitivity and Administration 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.

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 programme. Patients with pre-existing helminth infections should be treated for their infection prior to mepolizumab therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of *NUCALA* should be considered.

Interactions

No formal interaction studies have been performed with mepolizumab.

Pregnancy and Lactation

Fertility

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

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.

Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see *Non-Clinical Information*). The potential for harm to a human fetus is unknown.

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

Lactation

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

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.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of mepolizumab 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*.

Adverse Reactions

The safety of *NUCALA* was studied in a clinical development program in severe eosinophilic asthma which included 3 randomised, placebo-controlled, multicentre studies (n=1327). Subjects received either subcutaneous (SC) or intravenous (IV) mepolizumab or placebo during clinical studies of 24-52 weeks duration. Adverse reactions associated with *NUCALA* 100 mg administered subcutaneously (n=263) are presented in the table below. The safety profile of *NUCALA* in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1000).

System Organ Class	Adverse Reactions	Frequency
Infections & Infestations	Pharyngitis	Common
	Lower respiratory tract infection	Common
	Urinary tract infection	Common

System Organ Class	Adverse Reactions	Frequency
Nervous System Disorders	Headache	Very common
Respiratory, Thoracic & Mediastinal Disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back Pain	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
General disorders and administration site conditions	Pyrexia Local injection site reactions Administration-related reactions (systemic non-allergic)***	Common Common Common

*Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo. For examples of the associated manifestations reported and a description of the time to onset, see *Warnings and Precautions.*

**From spontaneous post-marketing reporting.

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

Description of selected adverse reaction

Local injection site reactions

In 2 placebo-controlled studies, the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

Paediatric population

The clinical trial data currently available in paediatric patients is too limited to characterise the safety profile of mepolizumab in this population (see *Pharmacodynamics*). However, the

frequency, type and severity of adverse reactions in the paediatric population are expected to be similar to those seen in adults.

Overdose

There is no clinical experience with overdose of *NUCALA*.

Single doses of up to 1500 mg of mepolizumab 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 mepolizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

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

R03DX09

Mechanism of action

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

Pharmacodynamic effects

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with *NUCALA*. The magnitude and duration of this reduction was dose-dependent. Following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, the blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment. This magnitude of blood eosinophils reduction was maintained in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. Overall, 15/260 (6%) of

subjects treated with 100 mg dose subcutaneously developed anti-mepolizumab antibodies after having received at least one dose of mepolizumab. The immunogenicity profile of mepolizumab in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

Neutralising antibodies were detected in one subject receiving mepolizumab. Anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab treatment in the majority of patients and there was no evidence of a correlation between antibody titres and change in eosinophil level.

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.

Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration (T_{max}) ranging from 4 to 8 days.

Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

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

Metabolism

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

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life (t1/2) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special Patient Populations

The population pharmacokinetics of mepolizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for race or gender.

Elderly patients (> 65 years old)

No formal studies have been conducted in elderly patients. However, in the population pharmacokinetic analysis, there was no indication of an effect of age on the pharmacokinetics of mepolizumab.

Paediatric population

There are limited pharmacokinetic data available in the paediatric population (59 subjects with eosinophilic esophagitis, 19 subjects with severe asthma). Of the 19 adolescents who received mepolizumab, 9 received *NUCALA* and the mean apparent clearance in these subjects was 35% less than that of adults.

Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in subjects aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account body weight. Mepolizumab pharmacokinetics in adolescent subjects with severe eosinophilic asthma included in the phase 3 studies were consistent with adults.

Renal impairment

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

Hepatic impairment

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

Clinical Studies

The efficacy of *NUCALA* in the treatment of a targeted group of subjects with severe eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These studies were designed to evaluate the efficacy of *NUCALA* administered once every 4 weeks by subcutaneous or intravenous injection in severe eosinophilic asthma patients not controlled on their standard of care [e.g., inhaled corticosteroids (ICS), oral corticosteroids (OCS), combination ICS and long-acting $beta_2$-adrenergic agonists (LABA), leukotriene modifiers, short-acting $beta_2$-adrenergic agonists (SABA)].

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1192 patients, 60% females, with a mean age of 49 years (range 12 - 82). The patients included in the Study MEA112997 and Study MEA115588 weigh ≥45kg. The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean

predicted pre-bronchodilator FEV1 was 60%. Patients continued to receive their existing asthma medicine during the studies.

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

Dose-ranging efficacy MEA112997 (DREAM) study

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

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

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

Exacerbation reduction (MEA115588) MENSA study

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

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

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

	NUCALA	Placebo

	(100 mg SC) N= 194	N= 191
Primary endpoint		
Frequency of Clinically Significant Exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-
p-value	<0.001	
Secondary endpoints		
Frequency of Exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of Exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	
Pre-bronchodilator FEV_1 (mL) at Week 32		
Mean Change from Baseline (SE)	183 (31.1)	86 (31.4)
Difference (mepolizumab vs. placebo)	98	
95% CI	11, 184	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Mean Change From Baseline (SE)	-16.0 (1.13)	-9.0 (1.16)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	-10.2, -3.8	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

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

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

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346

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

Oral Corticosteroid Reduction (MEA115575)

MEA115575 evaluated the effect of *NUCALA* 100 mg SC on reducing the use of maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe eosinophilic asthma who were dependent on systemic corticosteroids. Patients had a peripheral blood eosinophil count of ≥300/μL in the 12 months prior screening or a peripheral blood eosinophil count of ≥150/μL at baseline. Patients were administered *NUCALA* or placebo treatment once every 4 weeks over the treatment period. The OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained. During the study patients continued their baseline asthma therapy [i.e., high-dose inhaled corticosteroids (ICS) in combination with at least another controller such as long-acting $beta_2$-adrenergic agonists (LABA) or leukotriene modifiers].

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

The primary endpoint was the reduction in daily OCS dose (weeks 20-24) whilst maintaining asthma control compared with patients treated with placebo (see Table 4).

Table 4: Results of the primary and secondary endpoints in the Intent to Treat population (MEA115575)

	NUCALA (100 mg SC) N= 69	Placebo N= 66
Primary Endpoint		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
90% - 100% 75% - <90% 50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	16 (23%) 12 (17%) 9 (13%) 7 (10%) 25 (36%)	7(11%) 5 (8%) 10 (15%) 7(11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
Secondary Endpoints		
Reduction in the daily OCS dose (%)		
At least 50% reduction	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	
p-value	0.027	
Reduction in the daily OCS dose (%)		
To ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	

p-value	0.025	
Reduction in the daily OCS dose		
To 0 mg/Day	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0.414	
Median Percentage Reduction in Daily OCS Dose		
Median % reduction from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for *NUCALA* compared with placebo: -5.8 (95% CI: -10.6,-1.0; P=0.019). At Week 24, the proportion of subjects with a clinically meaningful decrease in SGRQ score (defined as a decrease of at least 4 units from baseline) was greater for *NUCALA* (58%, 40/69) compared with placebo (41%, 27/66).

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

Paediatric population

The safety and efficacy in paediatric patients younger than 12 years have not been established. There were 25 adolescents 13 girls and 12 boys, 9 aged 12 -14 years and 16 aged 15-17 years enrolled in study MEA115588. Of the total 25 subjects: 9 received placebo, 9 received mepolizumab 75 mg intravenously, and 7 received 100 mg subcutaneously. The same proportion of subjects (3/9) receiving placebo and mepolizumab intravenously reported clinically significant exacerbations; no exacerbations were reported in those receiving mepolizumab subcutaneously.

Non-Clinical Information

Carcinogenesis/mutagenesis

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

Reproductive Toxicology

Fertility

No impairment of fertility was observed in a fertility and general reproduction toxicity study in mice performed with an analogous antibody that inhibits IL-5 in mice. This study did not include a littering or functional F1 assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/foetal and postnatal development (including immune function) of the offspring. Examinations for internal or skeletal malformations were not performed. Data in cynomolgus monkeys demonstrate that mepolizumab 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.

Animal toxicology and pharmacology

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

Eosinophils 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.

PHARMACEUTICAL INFORMATION

List of Excipients

Sucrose

Sodium phosphate dibasic heptahydrate

Polysorbate 80

Hydrochloric Acid

Shelf Life

The expiry date is indicated on the packaging.

Storage

Unopened Vial

The storage conditions are detailed on the packaging. Do not freeze.

Protect from light. Store in the original carton until use.

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.

Nature and Contents of Container

NUCALA is presented as a sterile lyophilised powder in a 10 mL type I glass vial with bromobutyl rubber (non-latex) stopper and a gray aluminium overseal with a plastic flip-cap. The drug is supplied in a single-use vial without a preservative.

Incompatibilities

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

Use and Handling

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY.

NUCALA is provided as a lyophilised powder in a single-use vial for subcutaneous injection only. *NUCALA* does not contain a preservative therefore reconstitution by a healthcare professional should be carried out under aseptic conditions.

Once reconstituted, *NUCALA* will contain a concentration of 100 mg/mL mepolizumab. The reconstituted solution of mepolizumab, if not used immediately, should be stored below 30°C, and should not be frozen. Any unused concentrate or solution remaining after 8 hours must be discarded.

Instructions for reconstitution of each vial

1. Reconstitute the contents of the vial with **1.2 mL of sterile Water for Injection** preferably using a 2 to 3 mL syringe and a 21 gauge needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab.

2. The stream of sterile Water for Injection should be directed vertically onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15 second intervals until the powder is dissolved.

   Note: 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 has been added, but it may take additional time.

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 solution for particulate matter and clarity prior to

use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be used.

5. The reconstituted solution of *NUCALA*, if not used immediately:
    - Store below 30°C
    - Discard if not used within 8 hours of reconstitution
    - Do not mix with other medications
    - Do not freeze

Instructions for administration of each 100mg dose

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

Disposal

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

Not all presentations are available in every country.

Product Registrant

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[GSK logo]