NUCALA

Mepolizumab

1. NAME OF THE MEDICINAL PRODUCT

NUCALA, powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

3. PHARMACEUTICAL FORM

Powder for solution for injection

Lyophilised white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

NUCALA is indicated as add-on maintenance treatment of severe eosinophilic asthma in patients 12 years and older.

4.2. Dosage and Administration

NUCALA should be administered by a health care professional.

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*).

4.3. Contraindications

Hypersensitivity to mepolizumab or to any of the excipients.

4.4. 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. 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).

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.

4.5. Interactions

No formal interaction studies have been performed with mepolizumab.

4.6. Fertility, Pregnancy and Lactation

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see *Pre-clinical Safety Data*).

Pregnancy

The effect of mepolizumab on human pregnancy is unknown. No treatment related effects on embryo-foetal or postnatal development have been shown in animal studies *(see Pre-clinical Safety Data).*

NUCALA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

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.

4.7. 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*.

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

System Organ Class	**Adverse Reactions**	**Frequency**
Infections & Infestations	Pharyngitis	Common
	Lower respiratory tract infection	Common
	Urinary tract infection	Common
Nervous System Disorders	Headache	Very common
Respiratory, Thoracic & Mediastinal Disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common

System Organ Class	Adverse Reactions	Frequency
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back Pain	Common
General disorders and administration site conditions	Pyrexia Injection site reactions*	Common Common

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

To report any side effect(s):	
Kingdom of Saudi Arabia	
-National Pharmacovigilance centre (NPC) • Fax: +966-11-205-7662 • Call NPC at +966-11-208222, Ext: 2353-2356-2317-2354-2334-2340 • Toll-free: 8002490000 • E-mail: npc.drug@sfda.gov.sa • Website: www.sfda.gov.sa/npc	**-GlaxoSmithKline - Head Office, Jeddah** • Tel: 00966(012)6536666 • Fax: 00966(012)6536660 • P.O Box 55850, Jeddah 21544, Saudi Arabia

4.9. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

ATC code

Pharmacotherapeutic group: Interleukin inhibitors

L04AC06

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.

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. 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.

5.2. 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 (12- 82 years of age) 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, 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)].

Placebo Controlled Studies

In MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 621 patients, results demonstrated that mepolizumab (75 mg, 250 mg or 750 mg) significantly reduced asthma exacerbations when administered intravenously compared to placebo. There was no statistically significant difference in effect seen between the 3 studied doses. Blood eosinophil counts greater than or equal to 150 cells/µl at screening; or blood eosinophils ≥300 cells/µl in the past 12 months predicted subjects who would benefit most from *NUCALA* therapy. Results from this study were used to determine dose selection for the studies using subcutaneous mepolizumab administration. *NUCALA* is not indicated for intravenous use, and should only be administered by the subcutaneous route.

Exacerbation Reduction (MEA115588)

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 eosinophilic asthma. This study evaluated the frequency of clinically significant exacerbations of asthma, defined as: worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits.
Patients were aged 12 years of age or older, with a history of two or more asthma exacerbations in the past 12 months and not controlled on their current asthma drug therapies [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]. Patients were allowed to be on oral corticosteroid therapy and continued to receive their existing asthma medication during the study. Severe eosinophilic asthma patients were identified by peripheral blood eosinophils greater than or equal to 150 cells/µl within 6 weeks of randomisation (first dose) or blood eosinophils greater than or equal to 300 cells/µl within the past 12 months of randomisation.

Patients received either *NUCALA* 100 mg administered subcutaneously (SC), mepolizumab 75 mg administered intravenously (IV), or placebo treatment once every 4 weeks over 32 weeks.
The primary endpoint, reduction in the frequency of clinically significant exacerbations of asthma was statistically significant ($p<0.001$). Table 1, provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 1: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

	NUCALA (100 mg SC) N= 194	Placebo N= 191
Primary endpoint		
Frequency of Clinically Significant Exacerbations		

Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-
p-value	<0.001	
Secondary endpoints		
Frequency of Exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of Exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	
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	

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 2).

Table 2: 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).

5.3. Pre-clinical Safety Data

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sucrose

Sodium phosphate dibasic heptahydrate

Polysorbate 80

Hydrochloric Acid

6.2. Incompatibilities

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

6.3. Shelf Life

The expiry date is indicated on the packaging.

6.4. Special Precautions for Storage

Unopened Vial

Store at between 2°C and 8°C.

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.

6.5. 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.

6.6. Instructions for Use/Handling

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

Reconstitution Instructions

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 21G 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 be discarded.
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

Administration

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

Not all presentations are available in every country.

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PATIENT INFORMATION LEAFLET

NUCALA

Mepolizumab

100 mg powder for injection

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions about your illness or your medicine, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What NUCALA is and what it is used for
2. Before you use NUCALA
3. How to use NUCALA
4. Possible side effects
5. How to store NUCALA
6. Further information
7. Information for healthcare professionals

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody,* a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** in adults and adolescents over 12 years of age.

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

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

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

2. Before you are given Nucala

You must not receive Nucala

- if you are **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

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

Take special care with Nucala

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

Tell your doctor or nurse if your asthma remains uncontrolled, or gets worse, after you start Nucala treatment.

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body.
If you may have had a similar reaction to any injection or medicine,

Tell your doctor before you are given Nucala.

Parasitic infections
Nucala may weaken your resistance to infections caused by parasites. If you have a parasitic infection, it should be treated before you start treatment with Nucala.
If you live in a region where these infections are common or if you are travelling to such a region:

Check with your doctor if you think any of these may apply to you.

Children

This medicine is not intended for use in **children below the age of 12 years**.

Other medicines and Nucala

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma

✘ **Don't suddenly stop taking** your preventer medicines for your asthma once you have started Nucala. These medicines (especially ones called *corticosteriods*) must be stopped gradually, under the direct supervision of your doctor and dependant on your response to Nucala.

Pregnancy and breast-feeding

If you are pregnant, if you think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use Nucala.

Driving and using machines

The possible side effects of Nucala are unlikely to affect your ability to drive or use machines.

3. How to use Nucala

Nucala is given to you by a doctor, nurse or healthcare professional, as an injection just under the skin (subcutaneously).

The recommended dose for adults and adolescents over 12 years of age is 100 mg. You will be given 1 injection every four weeks.

If a dose of Nucala is missed

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Don't stop Nucala without advice

Do not stop receiving injections of Nucala unless your doctor advises you to. Interrupting or stopping the treatment with Nucala may cause your asthma symptoms and attacks to come back.

➔If your asthma symptoms get worse while receiving injections of Nucala

Call your doctor.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by Nucala are usually mild to moderate but can occasionally be serious.

Very common side effects

These may affect **more than 1 in 10** people:

- headache

Common side effects

These may affect **up to 1 in 10** people:

- chest infection- symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)

- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

➔ **Tell your doctor or pharmacist** if any of the side effects listed becomes **severe or troublesome**, or if you notice any side effects not listed in this leaflet.

5. How to Store Nucala

- **Keep out of the sight and reach of children.**
- Do not take NUCALA after the expiry date shown on the pack.
- Store at between 2°C and 8°C.
- Do not freeze.
- Store in the original package to protect from light.
- If your doctor tells you to stop taking NUCALA, it is important to return any remnants which are left over to your pharmacist.
- Don't throw away any medicines in wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. This will help to protect the environment.

6. Further information

What Nucala contains

The active substance is mepolizumab. Each vial contains 100 mg of mepolizumab. After reconstitution, each ml of solution contains 100 mg mepolizumab.

The other ingredients are sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80.

What Nucala looks like and contents of the pack

Nucala is a lyophilised white powder supplied in a clear, colourless glass vial with a rubber stopper.

Nucala is available in a pack containing 1 single use vial or in multipacks with 3 individual single use vials.

7. Information for healthcare professionals

Step-by-step instructions for use and handling, reconstitution, and administration
Nucala is provided as a lyophilised, white powder in a single-use vial for subcutaneous injection only. Nucala does not contain a preservative therefore reconstitution should be carried out under aseptic conditions.
Once reconstituted, Nucala will contain a concentration of 100 mg/mL mepolizumab.
The solution for injection can be stored between 2°C to 30°C for no more than 8 hours.
Any unused concentrate or solution remaining after 8 hours must be discarded.

Instructions for reconstitution

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 21G needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

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

2. If a mechanical reconstitution device (swirler) is used to reconstitute Nucala, reconstitution can be accomplished by swirling at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1000 rpm for no longer than 5 minutes is acceptable.
3. Following reconstitution, Nucala should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must be discarded.
4. The reconstituted solution, if not used immediately must be:
    - Protected from sunlight
    - Stored below 30°C, not frozen
    - Discarded if not used within 8 hours of reconstitution

Instructions for administration

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

Disposal

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

GDS Version Number: 4
GDS Version Date: March 2016

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A*, Parma, Italy
Address: Strada Provinciale Asolana, 90, 43056 San Polo diTorrile,, Parma, Italy

Marketing Authorisation Holder:
GlaxoSmithKline Trading Services Limited*, Ireland
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For any information about this medicinal product, please contact:
GlaxoSmithKline - Head Office, Jeddah
Tel: +966(02)6536666
Fax: +966(02)6536660
P.O Box 55850, Jeddah 21544, Saudi Arabia.

To report any side effect(s):

Kingdom of Saudi Arabia
-National Pharmacovigilance centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2353-2354-2334-2340
- Toll-free: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

-GlaxoSmithKline - Head Office, Jeddah

- Tel: 00966(012)6536666
- Fax: 00966(012)6536660
- P.O Box 55850, Jeddah 21544, Saudi Arabia.

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- **Keep all medicine out of reach of children**

Council of Arab Health Ministers
Union of Arab Pharmacists