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

Severe Eosinophilic Asthma

NUCALA is indicated as add-on maintenance treatment of severe eosinophilic asthma in patients 6 years and older.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

NUCALA is indicated as add-on treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients.

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

Severe Eosinophilic Asthma

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 aged 6 to 11 years old:

Children weighing ≥ 40 kg

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

Children weighing < 40 kg

The recommended dose is 40 mg of NUCALA administered by subcutaneous (SC) injection once every 4 weeks

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

The safety and efficacy of NUCALA have not been established in children less than 6 years of age.

EGPA

It is recommended that the sites for each injection are separated by at least 5 cm (see Use and Handling).

The recommended dose is 300 mg of NUCALA administered by subcutaneous (SC) injection once every 4 weeks.

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. 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).

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

Severe asthma

The safety of *NUCALA* was studied in a clinical development program in adolescents and adults with 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. Thirty-six children (aged 6-11) with severe eosinophilic asthma received NUCALA for 12 weeks. After a treatment interruption of 8 weeks, 30 of these received NUCALA for a further 52 weeks. No additional adverse reactions were identified to those reported for the adolescent and adult severe asthma 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 (≥1/10000 to <1/1000).

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

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo.
**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.

EGPA

In a double-blind placebo controlled study in subjects with EGPA (NUCALA 300 mg n= 68, placebo n= 68) no additional adverse reactions were identified to those reported for the severe asthma studies.

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: 2317-2356-2340
- Reporting hotline: 19999

- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: saudi.safety@gsk.com
- Website: https://gskpro.com/en-sa/
- 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: 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 of reduction in the indicated populations described below were observed within 4 weeks of treatment and were maintained throughout the treatment period.

In patients with severe asthma (adults/adolescents) or COPD (adults), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 and 52 weeks respectively, the blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% and 79%compared to placebo, respectively. 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.

In children 6 to 11 years old with severe asthma, following either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 48 and 44 cells/µL, respectively with a reduction from baseline of 85% and 87%, respectively.

In patients with EGPA following a dose of 300 mg administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 38 cells/µL. There was a geometric mean reduction of 83% compared to placebo.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In subjects with severe asthma, COPD and EGPA who received at least one dose of 100 mg, 100 mg and 300 mg respectively, administered subcutaneously every four weeks, 15/260 (6%), 27/615 (4%) and 1/68 (1%) had detectable anti-mepolizumab antibodies. 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. In children 6 to 11 years with severe asthma following either 40 mg SC (for a weight < 40kg) or 100 mg SC (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study. Neutralising antibodies were detected in one adult subject with severe asthma. 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. Mepolizumab pharmacokinetics were consistent in subjects with asthma, COPD or EGPA. The exposure at 300 mg in subjects with EGPA was approximately three times that observed at 100 mg in subjects with severe asthma or COPD. In a PK comparability study conducted in healthy subjects, following administration of a single 100 mg subcutaneous dose, mepolizumab pharmacokinetics were comparable between formulations.

Absorption

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

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

Distribution

Following a single intravenous administration 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.

Children

Mepolizumab pharmacokinetics following subcutaneous administration in subjects 6 to 11 years old with severe asthma were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg .

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

Mepolizumab pharmacokinetics in children (6 to 17 years) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe asthma.

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

Severe asthma

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 616 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).

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.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52 week study which evaluated 136 patients ≥ 18 years old with relapsing or refractory EGPA and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg /day prednisolone/prednisone). Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy.

Patients received a 300 mg dose of NUCALA or placebo administered subcutaneously once every 4 weeks in addition to their background prednisolone/prednisone with or without immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator.

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

Remission

Compared with placebo, subjects receiving NUCALA 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of subjects receiving NUCALA 300 mg achieved remission at both Week 36 and Week 48 (Table 3).

Table 3: Analyses of Co-Primary Endpoints (ITT Population)

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

An odds ratio >1 favours NUCALA

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

Relapse

Compared with placebo, the time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalisation), was significantly longer for subjects receiving NUCALA 300 mg ($p<0.001$) Additionally, subjects

receiving NUCALA had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral Corticosteroid Reduction

Compared with placebo, subjects receiving NUCALA 300 mg had a lower average daily oral corticosteroid dose during Weeks 48 to 52 ($p < 0.001$). In the NUCALA 300 mg group, 12 subjects (18%) were able to taper completely off OCS therapy compared with 2 subjects (3%) in the placebo group.

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

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 gouge 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 100 mg dose

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

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

Not all presentations are available in every country.

Version number: GDS12/IPI12

Date of issue: 25 June 2019

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A*, Parma, Italy

Marketing Authorisation Holder:
Glaxo Saudi Arabia Ltd.*, Jeddah, Kingdom of Saudi Arabia.
*member of the GlaxoSmithKline group of companies