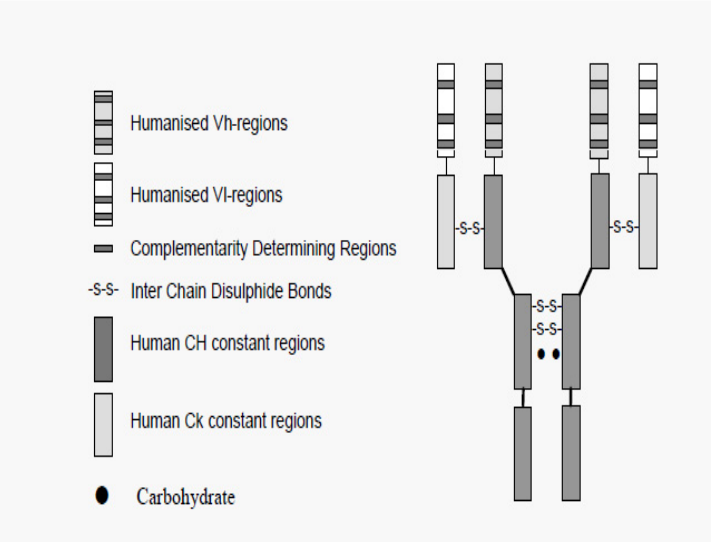
NUCALA®

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient of NUCALA is mepolizumab.

Structure of mepolizumab:



CAS number: 196078-29-2

DESCRIPTION

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against human interleukin-5 (IL-5). Mepolizumab is expressed as a soluble glycoprotein secreted from a recombinant Chinese hamster ovary cell line.

The total estimated molecular weight for mepolizumab is 149kDa.

NUCALA is a sterile lyophilised powder for injection in a single-use vial.

Each vial contains mepolizumab 100 mg (100 mg/mL after reconstitution). NUCALA also contains the excipients sucrose, dibasic sodium phosphate heptahydrate and polysorbate 80.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human 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 mepolizumab. The magnitude and duration of this reduction was dose-dependent. Following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, 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 and was maintained throughout the treatment period.

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 pharmacokinetic or pharmacodynamic effects 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 ($t_{1/2}$) 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 (65 years or older)

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 TRIALS

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 mepolizumab 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

Dose-Ranging Efficacy (MEA112997)

In study 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 mepolizumab therapy. Results from this study were used to determine dose selection for the studies using subcutaneous mepolizumab administration. Mepolizumab is not indicated for intravenous use, and should only be administered by the subcutaneous route.

Exacerbation Reduction (MEA115588)

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 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 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 was defined as 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 mepolizumab 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)

	Mepolizumab (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)

Study MEA115575 evaluated the effect of mepolizumab 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 cells/μL in the 12 months prior screening or a peripheral blood eosinophil count of ≥150 cells/μL at baseline. Patients were administered mepolizumab 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)

	Number (%) of Subjects	
	Mepolizumab (100 mg SC) N= 69	**Placebo N= 66**
Primary Endpoint:		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
n		
90% - 100%	16 (23%)	7(11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7(11%)
No decrease in OCS/lack of asthma control/ withdrawal from treatment	25 (36%)	37 (56%)
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 in daily OCS dose from baseline, n (%)	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	-
p-value	0.027	-
Reduction to ≤5 mg/day in daily OCS dose, n (%)	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	-
p-value	0.025	-
Reduction to 0 mg/day in daily OCS dose, n (%)	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	

OCS: prednisone/prednisolone

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 mepolizumab 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 mepolizumab (58%, 40/69) compared with placebo (41%, 27/66).

Open Label Extension Study (MEA115661)

Following completion of the double-blind MEA115575 and MEA115588 studies, all patients

were offered the opportunity to participate in MEA115661, a 52 week open-label extension (OLE) study, during which time all patients received open label mepolizumab (100mg SC). In total, 651 patients (126 subjects who had previously participated in study MEA115575 and 525 subjects who had previously participated in Study MEA115588), received 100 mg of mepolizumab subcutaneously every 4 weeks. During open-label treatment of all subjects with mepolizumab in MEA115661, the rates of exacerbations per year remained low in the subjects who were previously treated with mepolizumab and were consistent with results demonstrated during the 32-week double-blind period of study MEA115588. In addition, the impact of mepolizumab on steroid reduction was maintained following MEA115575 with average daily steroid dose remaining consistent with the level achieved with mepolizumab treatment at weeks 20-24 during MEA115575.

INDICATIONS

NUCALA is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over (see CLINICAL TRIALS).

CONTRAINDICATIONS

Hypersensitivity to mepolizumab or to any of the excipients (*see DESCRIPTION*).

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 (see ADVERSE EFFECTS). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

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 NUCALA therapy. If patients become infected whilst receiving treatment with NUCALA and do not respond to anti-helminth treatment, temporary discontinuation of NUCALA should be considered.

Opportunistic Infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with NUCALA versus none in the placebo group.

Effects on Fertility:

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

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

Use in Pregnancy (Category B1):

The effect of NUCALA on human pregnancy is unknown. No treatment related effects on embryofetal or postnatal development have been shown in animal studies.

In cynomolgus monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal and postnatal development (including immune function) of the offspring when given doses up to 100 mg/kg IV per month throughout gestation (yielding 31 times the AUC in humans at the clinical dose). 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.

In addition, in a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received a homologous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The homologous antibody did not produce obvious teratogenicity or otherwise affect embryo-fetal development in mice. Embryo-fetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

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

Use in Lactation:

There are no data regarding the excretion of NUCALA in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys postpartum following dosing during pregnancy 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.

Paediatric Use:

The safety and efficacy of NUCALA in children under the age of 12 years has not yet been established.

Use in the Elderly:

No formal studies have been conducted in elderly patients (see Pharmacokinetics –

Special Patient Populations).

Genotoxicity:

As mepolizumab is a monoclonal antibody, no genotoxicity studies have been conducted. Being a large protein molecule, mepolizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity:

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

Ability to Drive and Use Machines:

There have been no studies to investigate the effect of NUCALA on driving performance or the ability to operate machinery.

A detrimental effect on such activities would not be anticipated from the pharmacology or adverse reaction profile of NUCALA.

INTERACTIONS WITH OTHER MEDICINES

No formal interaction studies have been performed with NUCALA.

ADVERSE EFFECTS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions (*see* PRECAUTIONS*)*
- Opportunistic infections: herpes zoster *(see* PRECAUTIONS*)*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1,327 subjects with asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (MEA112997, MEA115588 and MEA115575). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose inhaled corticosteroids plus an additional controller(s) (MEA112997 and MEA115588), and 135 subjects required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s) to maintain asthma control (MEA115575). All subjects had markers of eosinophilic airway inflammation (*see* CLINICAL STUDIES*)*. Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg subcutaneous [SC]) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory

efficacy and safety trials (MEA115588 and MEA115575) with NUCALA is shown in Table 3.

Table 3: Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (MEA115588 and MEA115575)

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 263) %	Placebo (n = 257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from MEA112997 with 52 weeks of treatment with mepolizumab 75 mg intravenous (IV) (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 3 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Systemic Reactions, including Hypersensitivity Reactions

In MEA112997, MEA115588 and MEA115575 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-Term Safety

Nine hundred ninety-eight (998) subjects have received NUCALA in ongoing open-label extension studies, during which additional cases of herpes zoster have been reported. The overall adverse event profile was similar to the asthma trials described above.

Immunogenicity

Overall, 15/260 (6%) of subjects treated with NUCALA developed anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. Neutralizing antibodies were detected in 1 subject receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Post-marketing data

Adverse reactions are listed below by system organ class and frequency. The following convention has been used for the classification of adverse reactions:

Rare: ≥1/10,000 to <1/1,000.

System Organ Class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including anaphylaxis	Rare

DOSAGE AND ADMINISTRATION

NUCALA should be prescribed by a specialist experienced in the diagnosis and treatment of severe asthma.

NUCALA should be reconstituted and administered by a health care professional. In line with clinical practice, monitoring of patients after administration of biological agents is recommended (see PRECAUTIONS).

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

Adults and adolescents (12 years or older)

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

The safety and efficacy of NUCALA have not been established in adolescents weighing less than 45 kg.

Children (below 12 years)

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).

Use and Handling:

NUCALA is provided as a lyophilised powder in a single-use vial for subcutaneous injection only and should be reconstituted by a healthcare professional using standard aseptic techniques as follows:

Reconstitution Instructions

1. Reconstitute the NUCALA powder in the vial with 1.2 mL of sterile Water for Injections 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 Injections 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, followed by resting the vial for 5 seconds, 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.

   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 should not be used.

Reconstituted solution

NUCALA is for single use in one patient only and contains no antimicrobial agent. To reduce microbiological hazard, use as soon as practicable after reconstitution. Discard any unused solution.

If storage is necessary, store below 30°C for not more than 6 hours.

Administration

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 NUCALA 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.

OVERDOSAGE

There is no clinical experience with overdose of NUCALA.

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

There is no specific treatment for an overdose with NUCALA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Storage

Unopened vial

Store at 2°C - 8°C (Refrigerate. Do not freeze).

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

Reconstituted solution

After reconstitution with Water for Injections the product is stable for up to 6 hours when stored below 30°C.

Do not freeze.

During administration, protection from light is not necessary.

Nature and Contents of Container

NUCALA (mepolizumab) 100 mg powder for injection.

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. Each vial contains 144mg of mepolizumab (100 mg/mL after reconstitution with 1.2mL of WFI).

NUCALA is supplied in a pack containing one single use vial without a preservative.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 2 February 2016

DATE OF MOST RECENT AMENDMENT: 15 November 2016

NUCALA is a registered trade mark of the GSK group of companies.

Version 2.0