AUSTRALIAN PRODUCT INFORMATION

NUCALA (mepolizumab) powder for injection and solution for injection

1 NAME OF THE MEDICINE

Mepolizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Powder for injection

Each vial contains mepolizumab 100 mg (100 mg/mL after reconstitution).

Solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe)

Each pre-filled pen (auto-injector) or pre-filled syringe (safety-syringe) delivers 100 mg mepolizumab in 1 mL (100 mg/mL).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection

NUCALA is a sterile lyophilised white powder for injection in a single-use vial. It contains no preservative.

Solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe)

NUCALA is a clear to opalescent, colourless to pale yellow to pale brown solution in a single-use, pre-filled pen or syringe. It contains no preservative.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Severe eosinophilic asthma

NUCALA is indicated as an add-on treatment for severe eosinophilic asthma in patients aged 12 years and over (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Relapsed or refractory EGPA

NUCALA is indicated as an add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

NUCALA should be prescribed by a specialist physician, or a healthcare professional in consultation with a specialist physician, experienced in the diagnosis and treatment of severe asthma or EGPA.

NUCALA should only be administered as a subcutaneous (SC) injection (see Method of Administration below).

Powder for injection

NUCALA should be reconstituted and administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biological agents is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

NUCALA powder for injection 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.

Solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe)

NUCALA solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe) may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate and the patient or caregiver are trained in injection techniques.

NUCALA solution for injection is for single use in one patient only.

Dose

Severe eosinophilic asthma

Adults and adolescents (12 years or older)

The recommended dose is 100 mg of NUCALA administered by SC 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.

Relapsed or refractory EGPA

It is recommended that the sites for each injection are separated by at least 5 cm (see Method of administration below).

Adults (18 years or older)

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

Special populations

Elderly (65 years or older)

No dosage adjustment is recommended in patients 65 years or older *(*see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Patient Populations*)*.

Renal impairment

Dose adjustments in patients with renal impairment are unlikely to be required (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Patient Populations).

Hepatic Impairment

Dose adjustments in patients with hepatic impairment are unlikely to be required (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Patient Populations).

Method of administration

Powder for injection

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

Instructions for reconstitution of each vial

1. Reconstitute the NUCALA powder in the vial with 1.2 mL of sterile Water for Injection (WFI) 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 WFI 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 WFI 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

If storage is necessary, store below 25°C for not more than 6 hours.

Instructions for administration of each dose

1. For SC administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.

2. Just prior to administration, remove 1 mL of reconstituted NUCALA from one vial. **Do not shake** the reconstituted NUCALA solution during the procedure as this could lead to product foaming or precipitation. The residual solution remaining in the vial should be discarded with the vial.

3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) SC 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.

Solution for injection in pe-filled pen (auto-injector) or pre-filled syringe (safety syringe)

See the Instructions for Use leaflet for complete administration instructions with illustrations, which is appended to the CMI and available electronically at www.gsk.com.au/nucala or https://www.ebs.tga.gov.au/.

4.3 CONTRAINDICATIONS

Hypersensitivity to mepolizumab or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.8 ADVERSE EFFECTS [UNDESIRABLE 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 program. 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.

EGPA: Cessation of NUCALA

NUCALA treated patients may experience a return of EGPA symptoms upon cessation of NUCALA. As patients may decrease their other EGPA treatments during treatment with NUCALA, if NUCALA treatment is discontinued then other EGPA treatments may need to be increased accordingly.

Use in the Elderly

No formal studies have been conducted in elderly patients (see Section 5.2 PHARMACOKINETIC PROPERTIES, Special Patient Populations).

Paediatric Use

Severe eosinophilic asthma

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

Relapsed or refractory EGPA

The safety and efficacy of NUCALA in children under the age of 18 years has not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal interaction studies have been performed with NUCALA.

4.6 FERTILITY, PREGNANCY AND LACTATION

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

embryo-foetal or postnatal development have been shown in animal studies.

In cynomolgus monkeys, mepolizumab had no effect on pregnancy or on embryonic/foetal and postnatal development (including immune function) of the offspring when given doses up to 100 mg/kg IV per month throughout gestation (yielding 9 times the AUC in humans at the maximum recommended clinical dose of 300 mg SC once every 4 weeks). 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-foetal 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-foetal development in mice. Embryo-foetal 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 foetus.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

- Hypersensitivity reactions (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Opportunistic infections: herpes zoster (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Severe eosinophilic asthma

A total of 1,327 subjects with asthma were evaluated in 3 randomised, placebo-controlled, multicentre 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 enrolment despite regular use of high-dose inhaled corticosteroids (ICS) plus an additional controller(s) (MEA112997 and MEA115588), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus an additional controller(s) to maintain asthma control (MEA115575). All subjects had markers of eosinophilic airway inflammation (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered SC or intravenously (IV) once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg 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 1.

Table 1: 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 SC) (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 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 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnoea, 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 5% in the placebo group and 3% 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.

Relapsed or refractory EGPA

A total of 136 subjects with EGPA were evaluated in a double-blind, placebo-controlled study in which 300 mg mepolizumab (n=68) or placebo (n=68) was administered SC every 4 weeks for 13 treatments (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials). Approximately 3% of subjects receiving NUCALA withdrew due to adverse events compared with 2% of subjects receiving placebo. The following AEs were most commonly reported.

Table 2: Adverse Events with NUCALA with Greater than or Equal to 15% Incidence and More Common than Placebo in Subjects with EGPA (MEA115921)

Adverse Event	NUCALA (Mepolizumab 300 mg Subcutaneous) (n = 68) %	Placebo (n = 68) %
Any	90	96
Headache	32	18
Arthralgia	22	18
Nausea	19	16
Sinusitis	21	16
Upper respiratory tract infection	21	16
Diarrhoea	18	12
Vomiting	16	6
Injection site reaction	15	13

Immunogenicity

In subjects with severe asthma and EGPA who received at least one dose of 100 mg and 300 mg mepolizumab respectively, administered subcutaneously every four weeks15/260 (6%) and 1/68 (1%) respectively, had detectable anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration.

Neutralising antibodies were detected in one adult subject with severe asthma receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titres 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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no clinical experience with overdose of NUCALA.

Single doses of up to 1500 mg IV were administered 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Severe eosinophilic asthma

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 (SC) 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.

Relapsed or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA)

In a study in adult patients with EGPA following a dose of 300 mg administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 cells/µL (n=68) to 38 cells/µL (n=64) at week 52. There was a geometric mean reduction of 83% compared to placebo and 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. In subjects with severe asthma and EGPA who received at least one dose of 100 mg and 300 mg mepolizumab respectively, administered subcutaneously every four weeks, 15/260 (6%) and 1/68 (1%) respectively, had detectable anti-mepolizumab antibodies.

Neutralising antibodies were detected in one adult subject with severe asthma 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.

Clinical Trials

Severe eosinophilic 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 mepolizumab administered once every 4 weeks by SC or IV injection in severe eosinophilic asthma patients not controlled on their standard of care [e.g., ICS, 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 IV 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 SC mepolizumab administration. Mepolizumab is not indicated for IV use, and should only be administered by the SC 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 ICS in combination with at least another controller such as 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 SC, mepolizumab 75 mg 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 3 provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 3: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

	Mepolizumab (100 mg SC)	**Placebo**
	N=194	**N=191**
Primary endpoint		
Frequency of Clinically Significant Exacerbations		
Exacerbation rate per year	0. 83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-

	Mepolizumab (100 mg SC)	Placebo
	N=194	N=191
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 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 ICS in combination with at least another controller such as LABA or leukotriene modifiers).

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

The primary endpoint was the reduction in daily OCS dose (Weeks 20-24) whilst

maintaining asthma control compared with patients treated with placebo (see Table 4).

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

	Number (%) of Subjects	
	Mepolizumab (100 mg SC)	**Placebo**
	N= 69	**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 (100 mg 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 SC of mepolizumab 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.

Relapsed or refractory EGPA

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 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).

Patients received a 300 mg dose of mepolizumab 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.

A total of 136 subjects were enrolled. Demographic and disease characteristics were balanced between the treatment groups. The mean age was 48.5 years (17 subjects were aged 65 years or more); 59% were female; and 92% white. The mean duration of EGPA was 5.5 years (SD 4.63) and 74% had had one or more confirmed relapse in the past 2 years. The median baseline daily oral corticosteroid dose was 12 mg (prednisone or prednisolone equivalent) (range 7.5 to 50 mg) and 53% (n=72) were receiving other immunosuppressant therapy (e.g., azathioprine, methotrexate, mycophenolic acid.)

Remission

Compared with placebo, subjects receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of subjects receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (see Table 5).

Table 5: Analyses of Co-Primary Endpoints (ITT Population)

	Number (%) of Subjects	
	Placebo	**Mepolizumab 300 mg**
	N=68	**N=68**
Accrued Duration of Remission Over 52 Weeks		
0 weeks	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)

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

An odds ratio >1 favours mepolizumab

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day. There was a greater accrued time in remission in the mepolizumab group compared with placebo, in subjects with a baseline blood eosinophil count (BEC) ≥150 cells/µL.

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 mepolizumab 300 mg ($p<0.001$). Additionally, subjects receiving mepolizumab 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 mepolizumab 300 mg had a lower average daily oral corticosteroid dose during Weeks 48 to 52 ($p<0.001$). In the mepolizumab 300 mg group, 30 subjects (44%) were able to taper OCS therapy to ≤ 4 mg daily, compared with 5 subjects (7%) in the placebo group and 12 subjects compared to 2 were able to taper completely off OCS therapy.

Real-World Use Studies

Two open-label, single-arm, multi-dose, multicenter, 12-week studies were conducted to investigate the real-world use of a safety syringe (Study 205667) and an autoinjector (Study 204959) in subjects greater than 12 year of age with severe eosinophilic asthma. In Study 205667, 100% of subjects successfully self-administered mepolizumab in a safety syringe at week 8 (primary endpoint). In Study 204959, 98% of subjects successfully self-administered mepolizumab in an autoinjector at week 8 (primary endpoint).

5.2 PHARMACOKINETIC PROPERTIES

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. A Population pharmacokinetic analysis of the phase III EGPA study data (sparse pharmacokinetic samples) showed that mepolizumab pharmacokinetics in subjects with EGPA

were consistent with the pharmacokinetics in subjects with other eosinophilic conditions, including asthma. The exposure at 300 mg in subjects with EGPA was approximately three times that observed at 100 mg in subjects with severe asthma.

In a pharmacokinetic (PK) comparability study conducted in healthy subjects, following administration of a single 100 mg subcutaneous dose, mepolizumab pharmacokinetics were comparable between the powder for injection and solution for injection formulations.

Absorption

Following SC 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 SC 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 SC in the arm ranged from 74-80%. Following repeat SC administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single IV 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.

Excretion

Following a single IV 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 ($t_{1/2}$) of approximately 20 days. Following SC administration of mepolizumab the mean terminal half-life 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.

<u>Elderly (65 years or older)</u>

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.

<u>Renal impairment</u>

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.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Powder for injection

NUCALA powder for injection also contains the excipients sucrose, dibasic sodium phosphate heptahydrate, polysorbate 80 and water for injections.

Solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe)

NUCALA solution for injection also contains the excipients sucrose, dibasic sodium phosphate heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate and water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Powder for injection

Unopened vial

Refer to the product carton for storage conditions which will state either:

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

OR

“Store below 25°C (Do not freeze)”.

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

Reconstituted solution

After reconstitution with WFI, the product is stable for up to 6 hours when stored below 25°C.

Do not freeze.

During administration, protection from light is not necessary.

Solution for injection in pre-filled pen (auto-injector) and pre-filled syringe (safety-syringe)

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

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

The pre-filled pen and pre-filled syringe can be removed from the refrigerator and kept in the unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.

The pre-filled pen or pre-filled syringe must be administered within 8 hours once the pack is opened. Discard if not administered within 8 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

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 grey aluminium overseal with a plastic flip-cap. Each vial contains 144 mg of mepolizumab (100 mg/mL after reconstitution with 1.2 mL of WFI).

NUCALA is supplied in a pack containing one single use vial. Please note that WFI is not included in the pack.

Solution for injection in pre-filled pen (auto-injector)

NUCALA is presented as a 1 mL siliconised Type 1 glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled as an auto-injector.

NUCALA is supplied in a pack containing one single use pre-filled pen (auto-injector).

Solution for injection in pre-filled syringe (safety syringe)

NUCALA is presented as a 1 mL siliconised Type 1 glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled with a needle guard.

NUCALA is supplied in a pack containing one single use pre-filled syringe (safety syringe).

Not all dose forms or container types may be distributed in Australia.

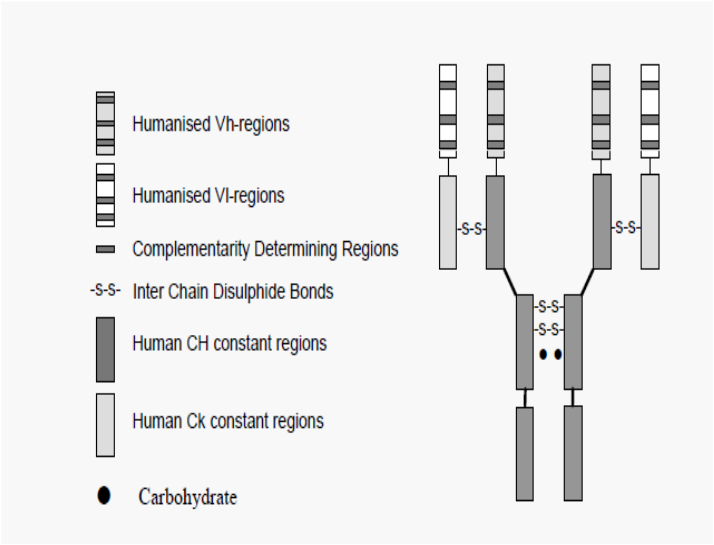
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Structure of mepolizumab:



The total estimated molecular weight for mepolizumab is 149 kDa.

CAS number

196078-29-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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

9 DATE OF FIRST APPROVAL

2 February 2016

10 DATE OF REVISION

2 December 2019

Summary table of changes

Section changed	Summary of new information
2, 3, 4.2, 5.1, 5.2, 6.4, 6.5	Update to include reference to the pre-filled pen (auto-injector) and pre-filled syringe (safety syringe) presentations.
4.4, 8, 10	Minor editorial changes

Version 6.0