SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.4 mL pre-filled syringe contains 40 mg of mepolizumab.
Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
A clear to opalescent, colourless to pale yellow to pale brown solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in children aged 6 to 11 years old (see section 5.1).

4.2 Posology and method of administration

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma.
Posology

Children aged 6 to 11 years old

The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient’s disease severity and level of control of exacerbations.

Special populations

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Children aged 6 to 11 years old

Nucala 100 mg powder for solution for injection and 40 mg solution for injection in pre-filled syringe are appropriate for administration to this population.

Nucala 100 mg solution for injection in pre-filled pen and 100 mg solution for injection in pre-filled syringe are not indicated for administration to this population.

Children less than 6 years old

The safety and efficacy of mepolizumab in children less than 6 years old have not yet been established.

No data are available.

Method of administration

The pre-filled syringe should be used for subcutaneous injection only.

Nucala must be administered by a healthcare professional or a caregiver. It may be administered by a caregiver if a healthcare professional determines that it is appropriate, and the caregiver is trained in injection techniques.

The recommended injection sites are the upper arm, abdomen or thigh.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled syringe are provided in the instructions for use in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

Asthma-related adverse symptoms or exacerbations may occur during treatment. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of mepolizumab therapy is not recommended. Reduction in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

Hypersensitivity and administration-related reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment (see section 4.8). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose,that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors

on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.
Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.
As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy. Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

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

A decision must be made whether to discontinue breast-feeding or to discontinue Nucala therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Nucala has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Severe eosinophilic asthma

In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

CRSwNP

In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were headache (18%) and back pain (7%).

EGPA

In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES

In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n= 263), from a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), in patients with EGPA receiving mepolizumab 300 mg SC (n=68), in a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years).

The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

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); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis Herpes zoster**	Common Uncommon
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare

System Organ Class	Adverse reactions	Frequency
Nervous system disorders	Headache	Very common
Respiratory, thoracic and 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 Arthralgia**	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 in the severe eosinophilic asthma studies. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

**From spontaneous post marketing reporting.
*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reactions

Systemic reactions, including hypersensitivity reactions, in CRSwNP

In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving mepolizumab 100 mg and in 1 patient (<1%) in the placebo group.

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic non-allergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local

injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In the placebo-controlled study, local injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.

EGPA

In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

Paediatric population

Severe eosinophilic asthma

Thirty-seven adolescents (aged 12-17) were enrolled in four placebo-controlled studies (25 mepolizumab treated intravenously or subcutaneously) of 24 to 52 weeks duration. Thirty -six paediatric patients (aged 6-11) received mepolizumab subcutaneously in an open-label study for 12 weeks. After a treatment interruption of 8 weeks, 30 of these patients, received mepolizumab for a further 52 weeks. The safety profile was similar to that seen in adults. No additional adverse reactions were identified.

HES

Four adolescents aged 12 to 17 years were enrolled in the placebo-controlled study 200622, one adolescent received 300 mg of mepolizumab, and 3 adolescents received placebo for 32 weeks. All 4 adolescents continued into a 20-week open-label extension study 205203 (see Section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via:

United Kingdom
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses of up to 1,500 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 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 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: 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 patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/µL at week 32 (n=182), a reduction of 84% compared to placebo. This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic 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 aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.
In adults, adolescents and children, 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 the placebo-controlled trials, 15/260 (6%) of adults and

adolescents with severe refractory eosinophilic asthma treated with 100 mg dose subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.
The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) was similar to that observed in the placebo-controlled studies.
In children aged 6 to 11 years old with severe refractory eosinophilic asthma following either 40 mg subcutaneously (for a weight < 40kg) or 100 mg subcutaneously (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab 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 patient with severe refractory eosinophilic asthma. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Clinical efficacy

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory 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 patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting $beta_2$ -adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV_1 was 60%. Patients continued to receive their existing asthma medicinal product during the studies**.**

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

Dose-ranging efficacy MEA112997 (DREAM) study

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

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

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

Exacerbation reduction MEA115588 (MENSA) study

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

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

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

	Mepolizumab 100 mg (subcutaneous) 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	

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
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		
Baseline (SD)	1730 (659)	1860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19. 5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

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

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

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/μL		
n	123	66
Exacerbation rate per year	1.16	1.73

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

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of ≥150/µL at baseline or a blood eosinophil count of ≥300/µL in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicinal product during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

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

The primary endpoint was the percent reduction in daily OCS dose (weeks 20-24), whilst maintaining asthma control by defined dose reduction categories (see Table 4). Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the prednisone dose from the end of the optimisation phase. The comparison between mepolizumab and placebo was statistically significant (p=0.008).

Table 4: Results of the primary and secondary endpoints in MEA115575

	ITT Population

	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
Primary endpoint		
Percent reduction in OCS from baseline (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 (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0. 414	
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	
Median % reduction in daily OCS dose 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	

Open-label extension studies in severe refractory eosinophilic asthma MEA115666 (COLUMBA), MEA115661 (COSMOS) and 201312 (COSMEX)

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

Paediatric population

In MEA115588 and in the double-blind placebo-controlled study 200862, there were 34 adolescents (12 to 17 years old). Of these 34 subjects: 12 received placebo, 9 received mepolizumab 75 mg intravenously, and 13 received 100 mg subcutaneously. In a combined analysis of these studies, a 40% reduction in clinically significant exacerbations was observed in adolescents following mepolizumab treatment compared to placebo (rate ratio 0.60; 95% CI: 0.17, 2.10).

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. Following administration of a single 100 mg subcutaneous dose in healthy subjects, mepolizumab systemic exposure was 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 to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

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 populations

Elderly patients (≥65 years old)

There are limited pharmacokinetic data available in elderly patients (≥65 years old) across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12 to 82 years.

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.

Paediatric population

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma)**.** Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in patients aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in adolescent patients with severe refractory eosinophilic asthma included in the phase 3 studies were consistent with adults (see section 4.2).

Paediatric pharmacokinetics following subcutaneous administration in patients 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics 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.

5.3 Preclinical safety data

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

Animal toxicology and/or 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 are thought to be 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. The relevance of these findings for humans is unknown.

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 offspring assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal 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 crossed the placenta. Concentrations of mepolizumab were about 1.2-2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Polysorbate 80
Disodium edetate
Water for injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

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

The pre-filled syringe(s) must be administered within 8 hours once the pack is opened. The pack should be discarded if not administered within 8 hours.

6.5 Nature and contents of container

0.4 mL solution in a 1 mL Type 1 glass syringe with a fixed needle (stainless steel) and passive safety needle guard.

Pack sizes:
1 pre-filled syringe
Multipack containing 3 (3 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Before administration, the solution should be inspected visually. The liquid should be clear to opalescent, colourless to pale yellow to pale brown. If the solution is cloudy, discoloured or contains particles, the solution should not be used.
After removing the pre-filled syringe(s) from the refrigerator, allow the syringe(s) to reach room temperature for at least 30 minutes before injecting Nucala.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled syringe(s) are provided at the end of the package leaflet.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited
79 New Oxford Street
London
WC1A 1DG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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