ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Lyophilised white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (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

Adults and adolescents aged 12 years and older
The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

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

Paediatric population

The posology of Nucala in children and adolescents aged between 6 to 17 years old with severe refractory eosinophilic asthma has been determined by limited efficacy, pharmacokinetic and pharmacodynamic studies and supported by modelling and simulation data (see sections 5.1 and 5.2).

Elderly patients
No dose adjustment is required for elderly patients (see section 5.2).

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

Method of administration

Nucala is for subcutaneous injection only and should be administered by a healthcare professional. It may be injected into the upper arm, thigh, or abdomen.

The powder should be reconstituted prior to administration and the reconstituted solution should be used immediately. For instructions on the reconstitution of the medicinal product before administration, see section 6.6.

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

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

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

Nucala should not be used to treat acute asthma exacerbations.

Asthma-related adverse events 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.

Abrupt discontinuation of corticosteroids after initiation of Nucala 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 Nucala. 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).

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 Nucala and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

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 drug-drug 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 cynomolgous 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

Adults and adolescents

In clinical studies in subjects with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache, injection site reactions and back pain.

Tabulated list of adverse reactions

A total of 896 adults and 19 adolescent subjects with severe refractory eosinophilic asthma received either a subcutaneous or an intravenous dose of mepolizumab during three placebo-controlled clinical studies of 24 to 52 weeks duration. The table below presents the adverse reactions from the two placebo-controlled studies in patients receiving mepolizumab 100 mg subcutaneously (n=263).

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 & infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic 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	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. 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 were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reaction

Local injection site reactions

In 2 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.

Paediatric population

In a total of 37 adolescents (aged 12-17) enrolled in four placebo-controlled studies (25 mepolizumab treated intravenously or subcutaneously) of 24 to 52 weeks duration and in a total of 36 paediatric patients (aged 6-11) who received mepolizumab subcutaneously for 12 weeks in an open-label uncontrolled study, the adverse event profile was similar to that seen in adults. No additional adverse reactions were identified.

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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no clinical experience with overdose of mepolizumab.

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 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. In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 12 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 12 of 386 to 42 (n=22) following 40 mg (for a weight < 40kg) and 331 to 55 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 89% and 83%, 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 treated with 100 mg dose subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab. 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. Neutralising antibodies were detected in one adult subject. 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 medicine 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 medicine.

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	
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 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 medicine 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

	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	

Paediatric population

Severe refractory eosinophilic asthma
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.

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 humanized IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life (t1/2) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Paediatric population

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

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.

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
Polysorbate 80

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

After reconstitution

Chemical and physical stability of the reconstituted medicinal product have been demonstrated for 8 hours when stored below 30°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear, colourless 10 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with a plastic flip-cap containing 100 mg powder for solution for injection.

Pack sizes:
1 vial
Multipack comprising 3 (3 packs of 1) vials

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

Nucala does not contain a preservative therefore reconstitution should be carried out under aseptic conditions.

Instructions for reconstitution for each vial

1. **Reconstitute the contents of the vial with 1.2 mL of sterile water for injection** preferably using a 2 to 3 mL syringe and a 21 gauge needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

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

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

Instructions for administration of 100 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 1 mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.

3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Instructions for administration of 40 mg dose
1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 0.4mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation. Dispose of the remaining solution.
3. Administer the 0.4mL injection (equivalent to 40 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
Currabinny
Carrigaline
County Cork
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/001
EU/1/15/1043/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 December 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

GlaxoSmithKline LLC
893 River Road
Conshohocken,
PA 19428
United States

Or

Human Genome Sciences, Inc.
9911 Belward Campus Drive
Rockville, MD 20850
United States

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana N. 90,
Torrile, 43056,
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (INDIVIDUAL PACKS INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Do not freeze.
Store in the original container to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Ltd.
Currabinny
Co. Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON OUTER PACKAGING

MULTIPACK CARTON (3 PACKS OF 1 VIAL – WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
Multipack: 3 (3 packs of 1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
Do not freeze.
Store in the original container to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Ltd.
Currabinny
Co. Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (MULTIPACK ONLY WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg powder for solution for injection
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)

3. LIST OF EXCIPIENTS

Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80

4. PHARMACEUTICAL FORM AND CONTENTS

Component of a multipack, not to be sold separately.
Powder for solution for injection
1vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

Do not freeze.
Store in the original container to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Ltd.
Currabinny
Co. Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Nucala 100 mg powder for solution for injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nucala 100 mg powder for solution for injection
mepolizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

1. What Nucala is and what it is used for

Nucala contains the active substance **mepolizumab,** a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat **severe asthma** in adults, adolescents and children aged 6 and over.

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

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

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

2. What you need to know before you use Nucala

Do not use Nucala:
- if you are **allergic** to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
Talk to your doctor before using this medicine.

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

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

Allergic and injection site reactions
Medicines of this type *(monoclonal antibodies)* can cause severe allergic reactions when injected into the body (see section 4, 'Possible side effects').

If you may have had a similar reaction to any injection or medicine,

➔ **Tell your doctor before you are given Nucala**.

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

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

Children
This medicine is not intended for use in **children below 6 years of age.**

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

Other medicines for asthma

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

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

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

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

3. How to use Nucala

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

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

Children aged 6 to 11 years old
The recommended dose is 40 mg. You will be given 1 injection every four weeks.

If a dose of Nucala is missed
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Stopping treatment with Nucala

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

If your asthma symptoms get worse while receiving injections of Nucala

➔ Call your doctor.

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

4. Possible side effects

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

Allergic reactions
Some people may have allergic or allergic-like reactions. These reactions may be common (they can affect **up to 1 in 10 people).** They usually occur within minutes to hours after the injection, but sometimes symptoms can start up to several days later.

Symptoms can include:

- chest tightness, cough, difficulty breathing
- fainting, dizziness, feeling lightheaded (due to a drop in blood pressure)
- swelling of eyelids, face, lips, tongue or mouth
- hives
- rash

➔ **Seek medical attention immediately** if you think you (or your child) may be having a reaction.

If you (or your child) may have had a similar reaction to any injection or medicine,

➔ Tell your doctor before you are given Nucala

Other side effects include:

Very common side effects
These may affect **more than 1 in 10** people:

- headache

Common side effects
These may affect **up to 1 in 10** people:

- chest infection - symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urination, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare side effects
These may affect up to **1 in 1,000** people:

- Severe allergic reactions (*anaphylaxis*)

➔ **Tell your doctor or a nurse immediately** if you get any of these symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Nucala

Keep this medicine out of the sight and reach of children.

Do not use Nucala after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store below 25°C.
Do not freeze.
Store in the original package to protect from light.

6. Contents of the pack and other information

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

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

What Nucala looks like and contents of the pack

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

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

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Step-by-step instructions for use and handling, reconstitution, and administration
Nucala is provided as a lyophilised, white powder in a single-use vial for subcutaneous injection only. Nucala does not contain a preservative therefore reconstitution should be carried out under aseptic conditions.

Once reconstituted, Nucala will contain a concentration of 100 mg/mL mepolizumab. The solution for injection can be stored between 2°C to 30°C for no more than 8 hours. Any unused concentrate or solution remaining after 8 hours must be discarded.

The trade name (Nucala) and batch number of the administered product should be clearly recorded in the patient file.

Instructions for reconstitution for each vial

1. **Reconstitute the contents of the vial with 1.2 mL of sterile water for injection** preferably using a 2 to 3 ml syringe and a 21 gauge needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

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

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

Instructions for administration of 100 mg dose

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

Instructions for administration of 40 mg dose

1. For subcutaneous administration, a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 0.4mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation. Dispose of the remaining solution.
3. Administer the 0.4mL injection (equivalent to 40 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Disposal

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