

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
Nucala 100 mg solution for injection in pre-filled syringe
Nucala 40 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nucala 100 mg solution for injection in pre-filled pen

Each 1 ml pre-filled pen contains 100 mg of mepolizumab.

Nucala 100 mg solution for injection in pre-filled syringe

Each 1 ml pre-filled syringe contains 100 mg of mepolizumab.

Nucala 40 mg solution for injection in pre-filled syringe

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

Severe eosinophilic asthma

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).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (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, CRSwNP, EGPA or HES.

Posology

Severe eosinophilic asthma

Adults and adolescents aged 12 years and over

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.

CRSwNP

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

EGPA

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with EGPA was supported by modelling and simulation data (see section 5.2).

Children aged 6 to 11 years old weighing ≥ 40 kg

The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old weighing < 40 kg

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

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

Patients who develop life-threatening manifestations of EGPA should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

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

Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

Special populations

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).

Paediatric population

Severe eosinophilic asthma

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.

CRSwNP in children less than 18 years old

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

EGPA in children less than 6 years old

The safety and efficacy of mepolizumab has not been established in children below the age of 6 years old.

No data are available.

HES in children aged less than 18 years old

The safety and efficacy of mepolizumab in children and adolescents aged less than 18 years old have not yet been established.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Nucala 100 mg solution for injection in pre-filled pen or pre-filled syringe

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

Nucala 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.

For children aged 6 to 11 years old, administration must be carried out by a healthcare professional or a trained caregiver.

For self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject Nucala into the upper arm.

For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

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

Nucala 40 mg solution for injection in pre-filled syringe

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.

Organ threatening or life-threatening EGPA

Nucala has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section 4.2).

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES (see section 4.2).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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	Common
	Urinary tract infection	
	Pharyngitis	
	Herpes zoster**	
Immune system disorders	Hypersensitivity reactions (systemic allergic)*	Common
	Anaphylaxis**	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
	Arthralgia**	
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)***	Common
	Local injection site reactions	
	Pyrexia	

* 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 the national reporting system listed in Appendix V.

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

Severe eosinophilic asthma

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/ μ L 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/ μ L (n=10) following 100 mg (for a weight \geq 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.

CRSwNP

In patients with CRSwNP, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 390 (n=206) to 60 cells/ μ L (n=126), which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period of 52 weeks.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/ μ L (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.

HES

In patients with HES (adults/adolescents), following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1 460 (n=54) to 70 cells/ μ L (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, EGPA and HES

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, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults and adolescents with HES treated with 300 mg dose

of mepolizumab 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) or in HES patients (n=102) treated for 20 weeks in open-label extension studies 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 and in no patients with CRSwNP, EGPA or HES. 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

Severe eosinophilic asthma

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 beta₂-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 1 192 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 FEV₁<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 FEV₁ 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/ μ L at initiation of treatment or greater than or equal to 300 cells/ μ L 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	53%	-
Rate ratio (95% CI)	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	61%	-
Rate ratio (95% CI)	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	69%	-
Rate ratio (95% CI)	0.31 (0.11, 0.91)	
p-value	0.034	

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Pre-bronchodilator FEV₁ (mL) at week 32		
Baseline (SD)	1 730 (659)	1 860 (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)	---
\geq500 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 $\geq 150/\mu\text{L}$ at baseline or a blood eosinophil count of $\geq 300/\mu\text{L}$ 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%	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 (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 $\leq 5\text{mg/day}$	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.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Study 205687 (SYNAPSE) was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP.

Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥ 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.

Key baseline characteristics included total endoscopic NP score mean (SD) 5.5 (1.29), nasal obstruction VAS score mean (SD) 9.0 (0.83), overall VAS symptom score mean (SD) 9.1 (0.74), loss of smell VAS score mean (SD) 9.7 (0.72) and Sino-Nasal Outcome Test (SNOT-22) mean (SD) 64.1 (18.32). The geometric mean eosinophil count was 390 cells/mL (95% CI: 360, 420). In addition, 27% of patients had aspirin-exacerbated respiratory disease (AERD) and 48% of patients had at least 1 course of OCS for CRSwNP in the past 12 months.

Patients received a 100 mg dose of mepolizumab or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. The key secondary endpoint was the time to first NP surgery up to Week 52 (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [e.g. polypectomy] in the nasal cavity). Patients who received mepolizumab had significantly greater improvements (decreases) in total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo, and all secondary endpoints were statistically significant in favour of mepolizumab (see Table 5 and Figure 1).

Table 5: Summary of results for primary and secondary endpoints (intent to treat population)

	Placebo (N=201)	Mepolizumab 100 mg SC (N=206)
Co-primary endpoints		
Total endoscopic score at week 52^a		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52)^a		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%) ^d	73 (36)	124 (60)
Key secondary endpoint		
Time to first nasal polyps surgery		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) ^e		0.43 (0.25, 0.76)
p-value ^e		0.003
Other secondary endpoints		
Overall VAS score (Weeks 49-52)^a		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%) ^f	40	64
SNOT-22 total score at week 52^{a, g}		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-16.49 (-23.57, -9.42)
≥28-point improvement (%) ^f	32	54

Patients requiring systemic corticosteroids for nasal polyps up to Week 52		
Number of patients with ≥ 1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) ^h		0.58 (0.36, 0.92)
p-value ^h		0.020
Composite VAS score - nasal symptoms (Weeks 49-52) ^{a, i}		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-2.68 (-3.44, -1.91)
≥ 2 -point improvement (%) ^f	40	66
Loss of smell VAS score (Weeks 49-52) ^a		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-0.37 (-0.65, -0.08)
≥ 3 -point improvement (%) ^f	19	36

^a Patients with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty were assigned their worst observed score prior to study withdrawal.

^b Based on Wilcoxon rank-sum test.

^c Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

^d A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.

^e Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).

^f Threshold for improvement has been identified as a meaningful within-patient change for this assessment

^g Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.

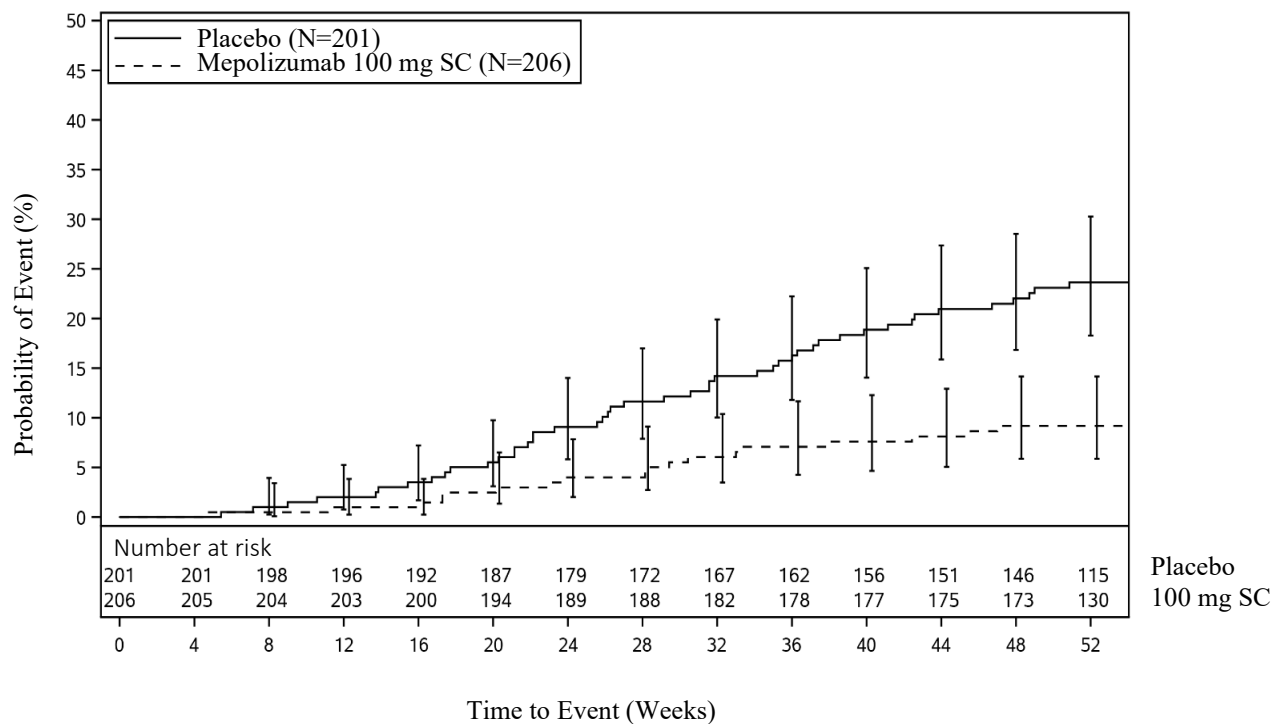
^h Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.

ⁱ Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.

Time to first NP surgery

Across the 52-week treatment period, patients in the mepolizumab group had a lower probability of undergoing NP surgery than patients in the placebo group. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; p=0.003).

Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps Surgery



A post-hoc analysis of the proportion of patients with surgery showed a 61% reduction in the odds of surgery versus placebo (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

CRSwNP patients with co-morbid asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for mepolizumab 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic granulomatosis with polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥ 7.5 to ≤ 50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life-threatening EGPA were excluded from study MEA115921.

Patients either 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.

Remission

The co-primary endpoints were the total accrued duration of remission, defined as a Birmingham Vasculitis Activity Score (BVAS) =0 plus prednisolone/prednisone dose ≤ 4 mg/day, and the

proportion of patients in remission at both 36 and 48 weeks of treatment. BVAS=0 represents no active vasculitis.

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 6).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

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

Table 6: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	Mepolizumab 300mg N=68
Accrued Duration of Remission Over 52 Weeks		
0	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
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
Patients 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. Remission: BVAS=0 and OCS dose ≤ 4 mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg ($p < 0.001$). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of ≤ 7.5 mg and ≤ 4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥ 12 years old with HES. Patients received 300 mg of mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.

Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count $\geq 1\ 000$ cells/ μL during screening. Patients who were FIP1L1-PDGFR α kinase-positive were excluded from the study.

The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥ 2 occasions).

The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 7). Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 2 and Table 8).

Table 7: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	Placebo N= 54
Proportion of patients who experienced a HES flare		
Patients with ≥ 1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥ 1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH =Cochran-Mantel-Haenszel

Time to first flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; $p=0.002$).

Figure 2: Kaplan Meier Curve for Time to First HES Flare

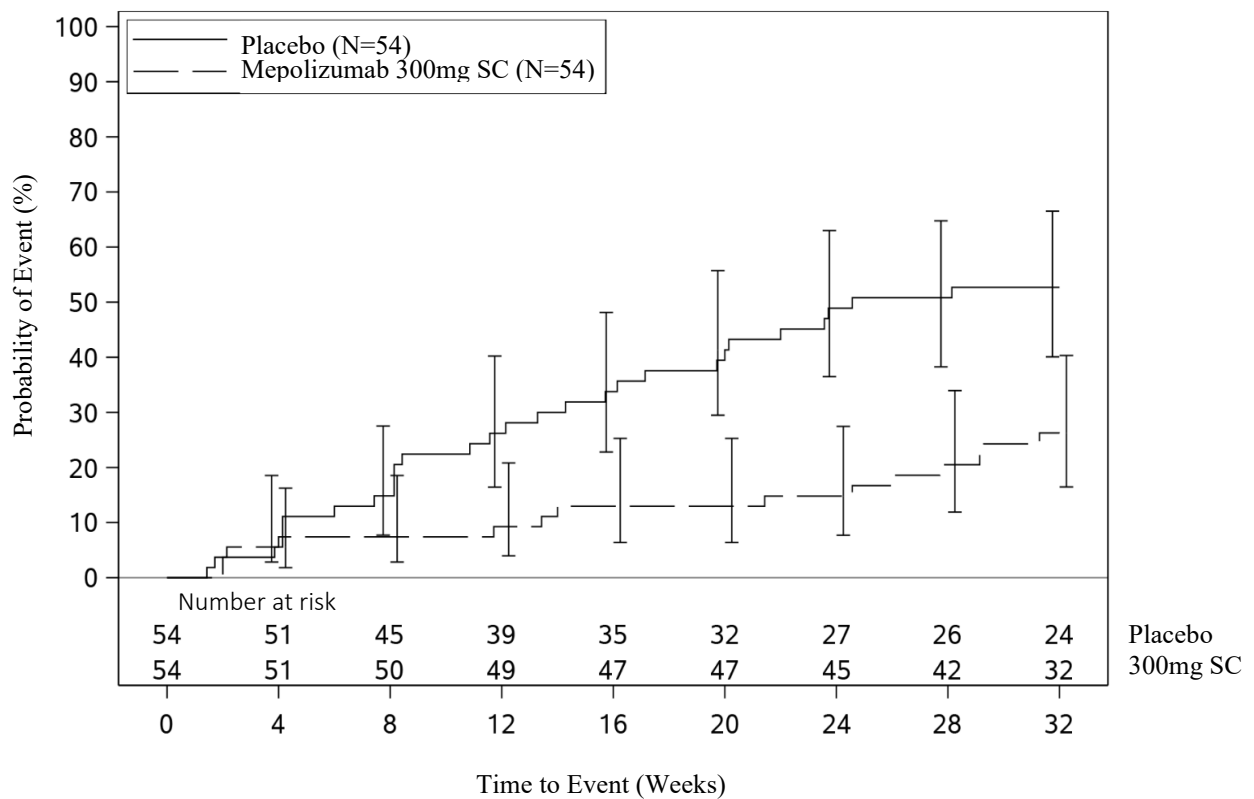


Table 8: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	Placebo N= 54
HES flares during week 20 and up to and including week 32		
Patients with ≥ 1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI) ^a	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32^b		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

^a rate ratio < 1 favours mepolizumab.

^b patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine

CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.

In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of $\geq 50\%$ during Weeks 16 to 20.

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).

Eosinophilic granulomatosis with polyangiitis (EGPA)

There are no clinical data available in children and adolescents aged 6 to 17 years old.

HES

Four adolescents (12 to 17 years old) were enrolled in study 200622; one adolescent received mepolizumab 300 mg, and 3 adolescents received placebo for 32 weeks. The one adolescent treated with mepolizumab in the 32-week Study 200622 did not have a HES flare. All 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 in which one of the 4 adolescents experienced one HES flare.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma and CRSwNP, 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

Severe eosinophilic asthma and HES

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma and 1 patient with HES). 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 or HES 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.

EGPA

Mepolizumab pharmacokinetics in children (6 to 17 years old) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe eosinophilic asthma. The recommended posology in children 6 to 11 years old over a 15-70 kg broad weight range predicts that the exposure would remain on average within 26% of adults at 300 mg.

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 compatibility 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 pen and 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 pen or 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

Nucala 100 mg solution for injection in pre-filled pen

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Pack sizes:

1 pre-filled pen
Multipack containing 3 (3 packs of 1) pre-filled pens
Multipack containing 9 (9 packs of 1) pre-filled pens

Not all pack-sizes may be marketed.

Nucala 100 mg solution for injection in pre-filled syringe

1 ml solution in a 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
Multipack containing 9 (9 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

Nucala 40 mg solution for injection in pre-filled syringe

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 and other handling

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 pen or pre-filled syringe(s) from the refrigerator, allow the pen or 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 pen or 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 Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Nucala 100 mg solution for injection in pre-filled pen

EU/1/15/1043/003 1 pre-filled pen

EU/1/15/1043/004 3 (3 x 1) pre-filled pens (multipack)

EU/1/15/1043/007 9 (9 x 1) pre-filled pens (multipack)

Nucala 100 mg solution for injection in pre-filled syringe

EU/1/15/1043/005 1 pre-filled syringe

EU/1/15/1043/006 3 (3 x 1) pre-filled syringes (multipack)

EU/1/15/1043/008 9 (9 x 1) pre-filled syringes (multipack)

Nucala 40 mg solution for injection in pre-filled syringe

EU/1/15/1043/009 1 pre-filled syringe

EU/1/15/1043/010 3 (3 x 1) pre-filled syringes (multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 December 2015

Date of latest renewal: 10 August 2020

10. DATE OF REVISION OF THE TEXT

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

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

Severe eosinophilic asthma

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).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate control.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (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, CRSwNP, EGPA or HES.

Posology

Severe eosinophilic asthma

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.

CRSwNP

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks.

EGPA

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with EGPA was supported by modelling and simulation data (see section 5.2).

Children aged 6 to 11 years old weighing ≥ 40 kg

The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old weighing < 40 kg

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

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

Patients who develop life-threatening manifestations of EGPA should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

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

Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

Special populations

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).

Paediatric population

Severe eosinophilic asthma

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.

Children aged 6 to 17 years old

The posology of mepolizumab in children and adolescents aged 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).

CRSwNP in children less than 18 years old

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established. No data are available.

EGPA in children less than 6 years old

The safety and efficacy of mepolizumab has not been established in children below the age of 6 years old.

No data are available.

HES in children aged less than 18 years old

The safety and efficacy of mepolizumab in children and adolescents aged less than 18 years old have not yet been established.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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.

For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

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 mepolizumab 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

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.

Organ threatening or life-threatening EGPA

Nucala has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section 4.2).

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES (see section 4.2).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ 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	Common
	Urinary tract infection	
	Pharyngitis	Uncommon
	Herpes zoster**	
Immune system disorders	Hypersensitivity reactions (systemic allergic)*	Common
	Anaphylaxis**	Rare
Nervous system disorders	Headache	Very common

System Organ Class	Adverse reactions	Frequency
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 the national reporting system listed in Appendix V.

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

Severe eosinophilic asthma

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/ μ L 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/ μ L (n=10) following 100 mg (for a weight \geq 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.

CRSwNP

In patients with CRSwNP, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 390 (n=206) to 60 cells/ μ L (n=126), which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period of 52 weeks.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/ μ L (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.

HES

In patients with HES (adults/adolescents), following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks

of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1 460 (n=54) to 70 cells/ μ L (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, EGPA and HES

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, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults and adolescents with HES treated with 300 mg dose of mepolizumab 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) or in HES patients (n=102) treated for 20 weeks in open-label extension studies 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 \geq 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 and in no patients with CRSwNP, EGPA or HES. 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

Severe eosinophilic asthma

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 beta₂-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 1 192 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 FEV₁<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 FEV₁ 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/ μ L at initiation of treatment or greater than or equal to 300 cells/ μ L 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	53%	-
Rate ratio (95% CI)	0.47 (0.35, 0.64)	
p-value	<0.001	
Secondary endpoints		

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Frequency of exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction	61%	–
Rate ratio (95% CI)	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	69%	–
Rate ratio (95% CI)	0.31 (0.11, 0.91)	
p-value	0.034	
Pre-bronchodilator FEV₁ (mL) at week 32		
Baseline (SD)	1 730 (659)	1 860 (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		

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
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)	---
\geq500 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 \geq 150/ μ L at baseline or a blood eosinophil count of \geq 300/ μ L 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%	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)	

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
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.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Study 205687 (SYNAPSE) was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP. Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.

Key baseline characteristics included total endoscopic NP score mean (SD) 5.5 (1.29), nasal obstruction VAS score mean (SD) 9.0 (0.83), overall VAS symptom score mean (SD) 9.1 (0.74), loss of smell VAS score mean (SD) 9.7 (0.72) and Sino-Nasal Outcome Test (SNOT-22) mean (SD) 64.1 (18.32). The geometric mean eosinophil count was 390 cells/mL (95% CI: 360, 420). In addition, 27% of patients had aspirin-exacerbated respiratory disease (AERD) and 48% of patients had at least 1 course of OCS for CRSwNP in the past 12 months.

Patients received a 100 mg dose of mepolizumab or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. The key secondary endpoint was the time to first NP surgery up to Week 52 (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [e.g. polypectomy] in the nasal cavity). Patients who received mepolizumab had significantly greater improvements (decreases) in

total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo, and all secondary endpoints were statistically significant in favour of mepolizumab (see Table 5 and Figure 1).

Table 5: Summary of results for primary and secondary endpoints (intent to treat population)

	Placebo (N=201)	Mepolizumab 100 mg SC (N=206)
Co-primary endpoints		
Total endoscopic score at week 52^a		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52)^a		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%) ^d	73 (36)	124 (60)
Key secondary endpoint		
Time to first nasal polyps surgery		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) ^e		0.43 (0.25, 0.76)
p-value ^e		0.003
Other secondary endpoints		
Overall VAS score (Weeks 49-52)^a		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%) ^f	40	64
SNOT-22 total score at week 52^{a, g}		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-16.49 (-23.57, -9.42)
≥28-point improvement (%) ^f	32	54

Patients requiring systemic corticosteroids for nasal polyps up to Week 52		
Number of patients with ≥ 1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) ^h		0.58 (0.36, 0.92)
p-value ^h		0.020
Composite VAS score - nasal symptoms (Weeks 49-52) ^{a, i}		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-2.68 (-3.44, -1.91)
≥ 2 -point improvement (%) ^f	40	66
Loss of smell VAS score (Weeks 49-52) ^a		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
p-value ^b		<0.001
Difference in medians (95% CI) ^c		-0.37 (-0.65, -0.08)
≥ 3 -point improvement (%) ^f	19	36

^a Patients with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.

^b Based on Wilcoxon rank-sum test.

^c Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

^d A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.

^e Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).

^f Threshold for improvement has been identified as a meaningful within-patient change for this assessment

^g Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.

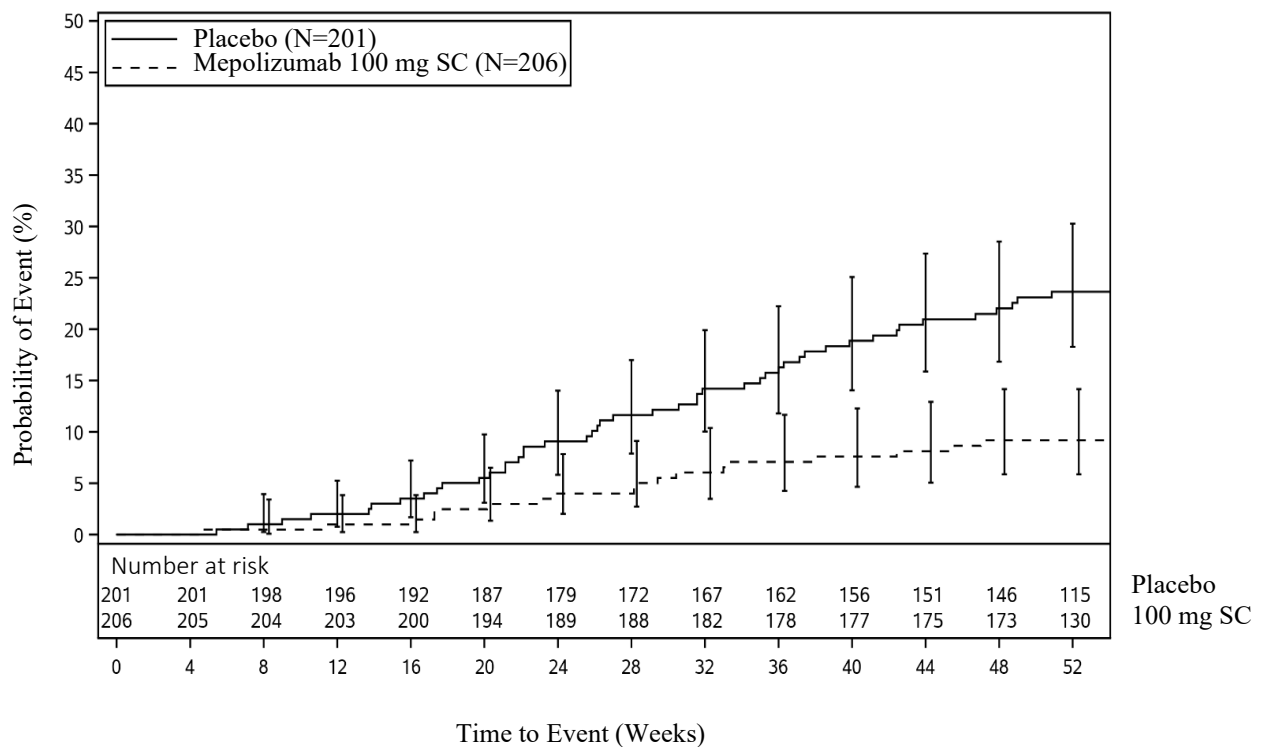
^h Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.

ⁱ Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.

Time to first NP surgery

Across the 52-week treatment period, patients in the mepolizumab group had a lower probability of undergoing NP surgery than patients in the placebo group. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; p=0.003).

Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps Surgery



A post-hoc analysis of the proportion of patients with surgery showed a 61% reduction in the odds of surgery versus placebo (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

CRSwNP patients with co-morbid asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for mepolizumab 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic granulomatosis with polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥ 7.5 to ≤ 50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life-threatening EGPA were excluded from study MEA115921.

Patients either 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.

Remission

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

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 6).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

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

Table 6: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	Mepolizumab 300mg N=68
Accrued Duration of Remission Over 52 Weeks		
0	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
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
Patients 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 Nucala. Remission: BVAS=0 and OCS dose ≤ 4 mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg ($p < 0.001$). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of ≤ 7.5 mg and ≤ 4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥ 12 years old with HES. Patients received 300 mg of mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.

Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥ 1000 cells/ μL during screening. Patients who were FIP1L1-PDGFR α kinase-positive were excluded from the study.

The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥ 2 occasions).

The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 7). Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 2 and Table 8).

Table 7: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	Placebo N= 54
Proportion of patients who experienced a HES flare		
Patients with ≥ 1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥ 1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH =Cochran-Mantel-Haenszel

Time to first flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with Nucala compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; p=0.002).

Figure 2: Kaplan Meier Curve for Time to First HES Flare

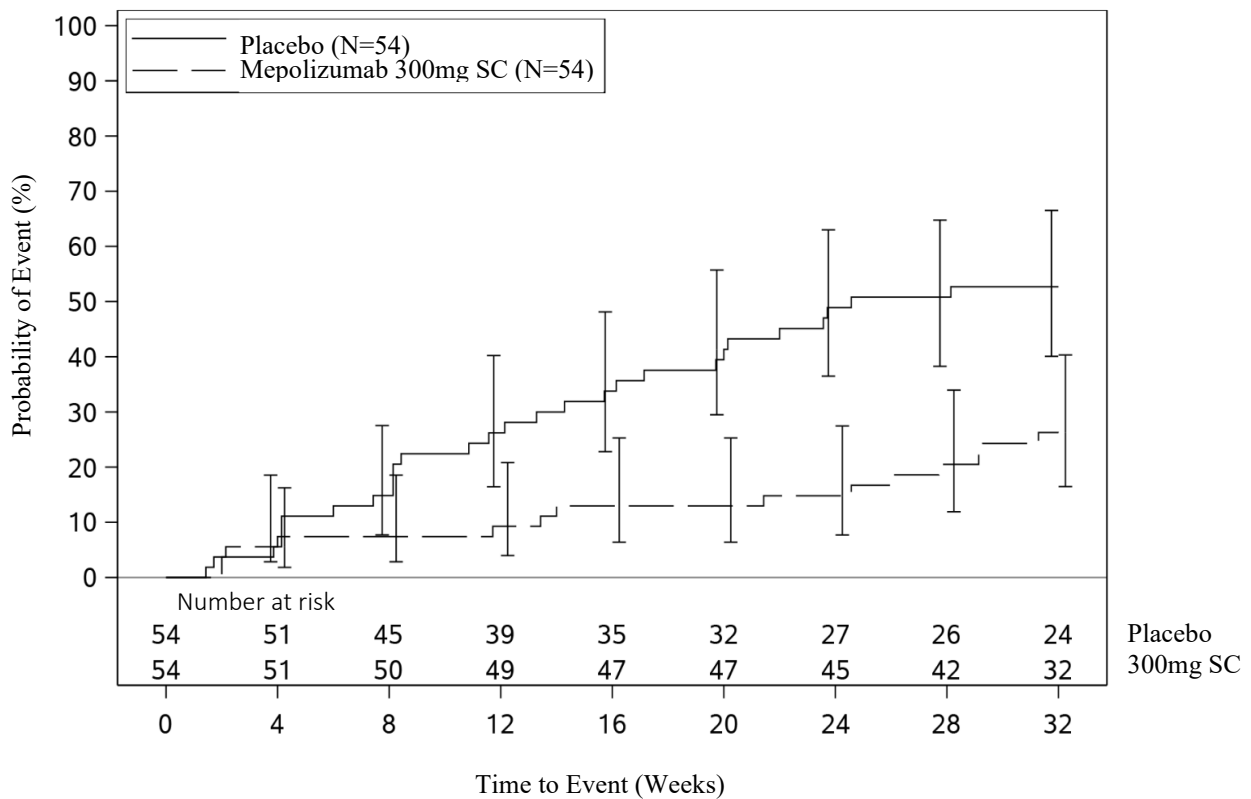


Table 8: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	Placebo N= 54
HES flares during week 20 and up to and including week 32		
Patients with ≥ 1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI) ^a	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32^b		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

^a rate ratio <1 favours mepolizumab.

^b patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine

CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.

In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of $\geq 50\%$ during Weeks 16 to 20.

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).

Eosinophilic granulomatosis with polyangiitis (EGPA)

There are no clinical data available in children and adolescents aged 6 to 17 years old.

HES

Four adolescents (12 to 17 years old) were enrolled in study 200622; one adolescent received mepolizumab 300 mg, and 3 adolescents received placebo for 32 weeks. The one adolescent treated with mepolizumab in the 32-week Study 200622 did not have a HES flare. All 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 in which one of the 4 adolescents experienced one HES flare.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma and CRSwNP, 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.

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

Severe eosinophilic asthma and HES

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma and 1 patient with HES). 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 or HES 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.

EGPA

Mepolizumab pharmacokinetics in children (6 to 17 years old) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe eosinophilic asthma. The recommended posology in children 6 to 11 years old over a 15-70 kg broad weight range predicts that the exposure would remain on average within 26% of adults at 300 mg.

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 containing 3 (3 packs of 1) vials

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 injections** 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 1 000 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.

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.

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
12 Riverwalk
Citywest Business Campus
Dublin 24
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

Date of latest renewal: 10 August 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://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 No. 90,
Torrile, 43056, Parma,
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 (PSURs)**

The requirements for submission of PSURs 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 (MAH) shall submit the first PSUR 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 marketing authorisation holder (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 – PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

1 pre-filled pen.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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

Do not freeze.

Store pen in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

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

OUTER CARTON FOR PRE-FILLED PEN MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen
Multipack: 3 (3 packs of 1) pre-filled pens
Multipack: 9 (9 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

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

Do not freeze.

Store pen in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/004 (3 x 1 pre-filled pens)

EU/1/15/1043/007 (9 x 1 pre-filled pens)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON - PRE-FILLED PEN MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen.

1 pre-filled pen. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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 in a refrigerator.

Do not freeze.

Store pen in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Nucala 100 mg injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 100 mg syringe

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

OUTER CARTON– FOR PRE-FILLED SYRINGE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 3 (3 packs of 1) pre-filled syringes

Multipack: 9 (9 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

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

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/006 (3 x 1 pre-filled syringes)
EU/1/15/1043/008 (9 x 1 pre-filled syringes)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

nucala 100 mg syringe

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON – PRE-FILLED SYRINGE MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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 in a refrigerator.

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 100 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

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

Nucala 100 mg injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe.

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 40 mg syringe

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

OUTER CARTON– FOR PRE-FILLED SYRINGE MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

Multipack: 3 (3 packs of 1) pre-filled syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

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

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1043/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

nucala 40 mg syringe

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 INTERMEDIATE PACKAGING

INTERMEDIATE CARTON – PRE-FILLED SYRINGE MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Nucala 40 mg solution for injection in pre-filled syringe
mepolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 mg mepolizumab.

3. LIST OF EXCIPIENTS

Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

1 pre-filled syringe. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use only.

PRESS HERE TO OPEN

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 in a refrigerator.

Do not freeze.

Store syringe in the original carton in order to protect from light.

Time out of refrigeration should not exceed a maximum of 7 days when protected from light and stored below 30°C.

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

nucala 40 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL**

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

Nucala 40 mg injection
mepolizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

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.

PRESS HERE TO OPEN

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
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.
12 Riverwalk
Citywest Business Campus
Dublin 24
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

Powder for solution for injection 1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

PRESS HERE TO OPEN

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.
12 Riverwalk
Citywest Business Campus
Dublin 24
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 solution for injection in pre-filled pen

mepolizumab

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
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

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** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

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

Severe eosinophilic asthma

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.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood, and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps. Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin.

Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids*, Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

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 and adolescents

Severe eosinophilic asthma

The pre-filled pen is not intended for use in **children below 12 years of age** for the treatment of severe eosinophilic asthma.

For children aged 6-11 years, contact your doctor who will prescribe the recommended dose of Nucala which will be administered by a nurse or doctor.

CRSwNP

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

EGPA

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

HES

This medicine is not intended for use in **adolescents or children below 18 years of age** for the treatment of HES.

Other medicines and Nucala

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

Other medicines for asthma, CRSwNP, EGPA or HES

- ✗ **Don't suddenly stop taking** your existing medicines for your asthma, CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent 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.

Nucala contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you or your caregiver can inject Nucala. If appropriate, they will then provide training to show you or your caregiver the correct way to use Nucala.

Nucala must be given to children aged 6 to 11 years by a doctor, nurse or trained caregiver.

Severe eosinophilic asthma

The recommended dose for adults and adolescents aged 12 years and older is 100 mg. You will have 1 injection every four weeks.

CRSwNP

The recommended dose for adults is 100 mg. You will have 1 injection every four weeks.

EGPA

The recommended dose for adults and adolescents aged 12 years and older is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:

The recommended dose is 200 mg. You will have 2 injections every four weeks.

Children weighing less than 40 kg:

The recommended dose is 100 mg. You will have 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

The recommended dose for adults is 300 mg. You will have 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

Instructions for using the pre-filled pen are given on the other side of this leaflet.

If you use more Nucala than you should

If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed

You or your caregiver should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time for your next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala

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

If your 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 may have had a similar reaction to any injection or medicine:

➔ **Tell your doctor** before you (or your child) are given Nucala.

Other side effects include:

Very common:

may affect more than 1 in 10 people

- headache

Common:

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 urine, 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
- arthralgia (joint pain)
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Uncommon:

may affect up to 1 in 100 people

- herpes zoster (shingles)

Rare:

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 in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

The Nucala pre-filled pen can be removed from the refrigerator and kept in its 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.

6. Contents of the pack and other information

What Nucala contains

The active substance is mepolizumab.

Each 1 mL pre-filled pen contains 100 mg of mepolizumab.

The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 1 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled pen.

Nucala is available in a pack containing 1 pre-filled pen, or in a multipack comprised of 3 x 1 pre-filled pens or 9 x 1 pre-filled pens.

Marketing Authorisation Holder

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, No 90
43056 San Polo di Torrile, Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0) 10 85 52 00

България

“Берлин-Хеми/А. Менарини
България” ЕООД
Тел.: + 359 2 454 0950
bcsofia@berlin-chemie.com

Česká republika

GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti

OÜ Berlin-Chemie Menarini Eesti
Tel: + 372 667 5001
ee@berlin-chemie.com

Ελλάδα

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε.
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska

Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: +385 1 4821 361
office-croatia@berlin-chemie.com

Lietuva

UAB “BERLIN-CHEMIE MENARINI BALTIC”
Tel: + 370 52 691 947
lt@berlin-chemie.com

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Magyarország

Berlin-Chemie/A. Menarini Kft.
Tel.: + 36 23501301
bc-hu@berlin-chemie.com

Malta

GlaxoSmithKline Trading Services Ltd.
Tel: + 356 80065004

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline Trading Services Ltd.
Tel: + 40 800672524

Ireland

GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland

Vistor hf.
Sími: + 354 535 7000

Italia

GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Κύπρος

GlaxoSmithKline Trading Services Ltd.
Τηλ: + 357 80070017

Latvija

SIA Berlin-Chemie/Menarini Baltic
Tel: + 371 67103210
lv@berlin-chemie.com

Slovenija

Berlin-Chemie / A. Menarini Distribution
Ljubljana d.o.o.
Tel: + 386 (0)1 300 2160
slovenia@berlin-chemie.com

Slovenská republika

Berlin-Chemie / A. Menarini Distribution
Slovakia s.r.o.
Tel: + 421 2 544 30 730
slovakia@berlin-chemie.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom (Northern Ireland)

GlaxoSmithKline Trading Services Ltd.
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

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

7. Step by step instructions for using the pre-filled pen

Administer once every four weeks.

Follow these instructions on how to use the pre-filled pen. Failure to follow these instructions may affect proper function of the pre-filled pen. You should also receive training on how to use the pre-filled pen. Nucala pre-filled pen is for use **under the skin only** (subcutaneous).

How to store Nucala

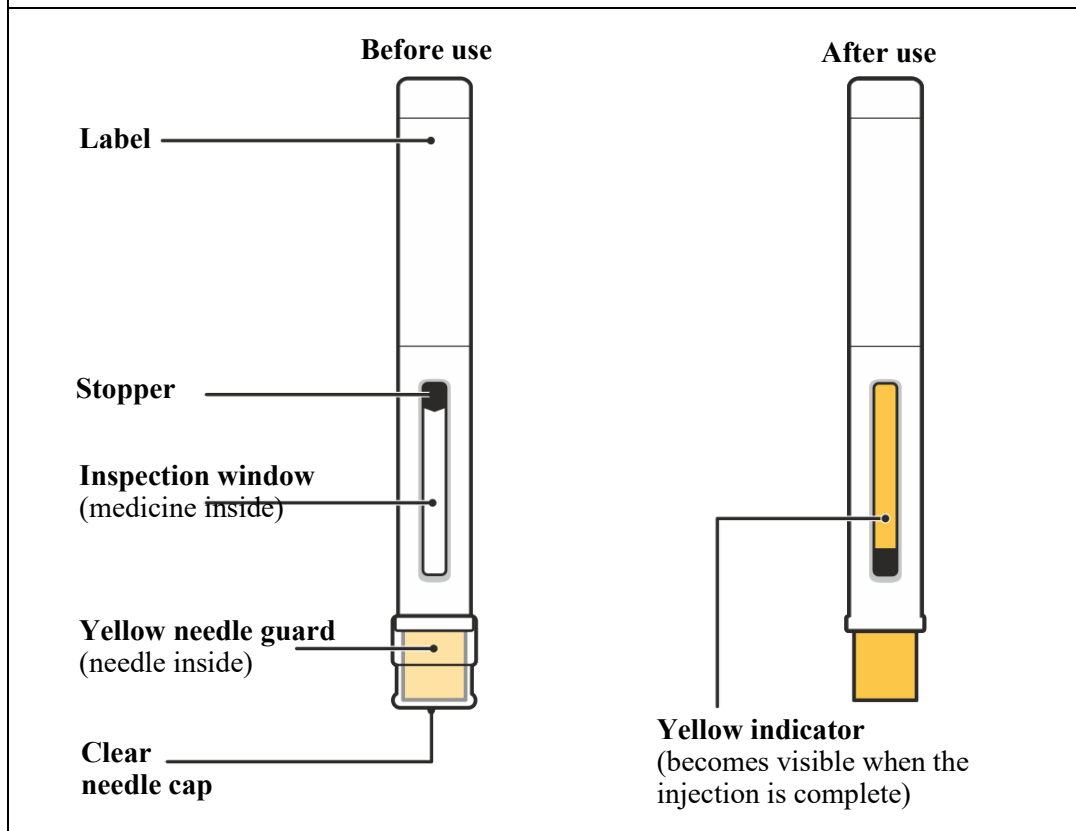
- Keep refrigerated before use.
- Do not freeze
- Keep the pre-filled pen in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled pen may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pen away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use Nucala

The pre-filled pen should be used only once and then discarded.

- **Do not** share your Nucala pre-filled pen with another person.
- **Do not** shake the pen.
- **Do not** use the pen if dropped onto a hard surface.
- **Do not** use the pen if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled pen



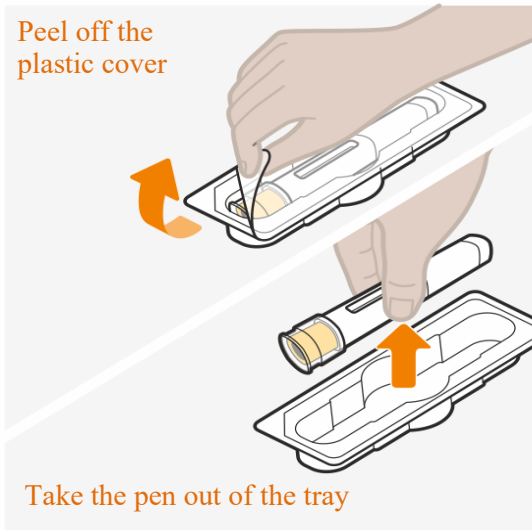
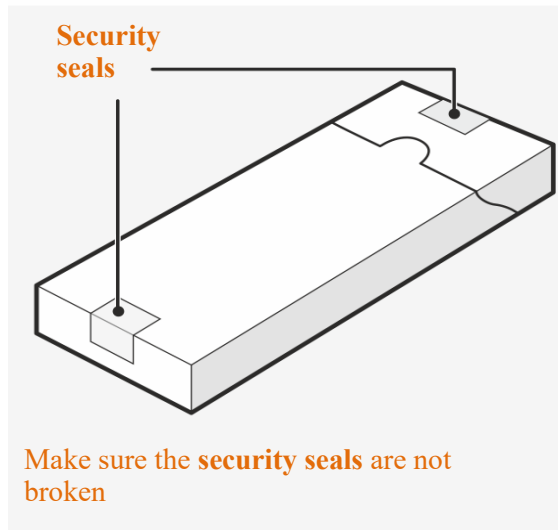
Prepare

1. Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled pen
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

2. Take out your pre-filled pen

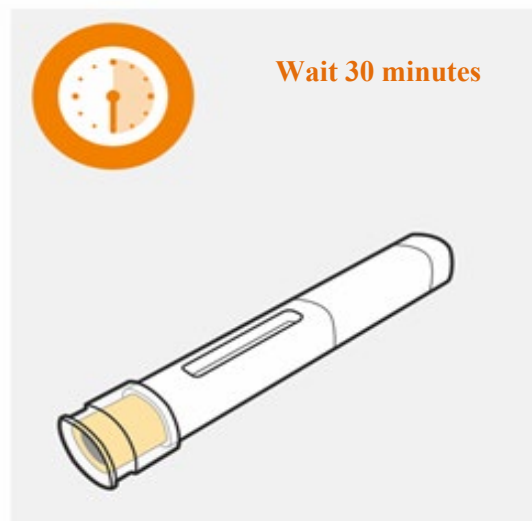
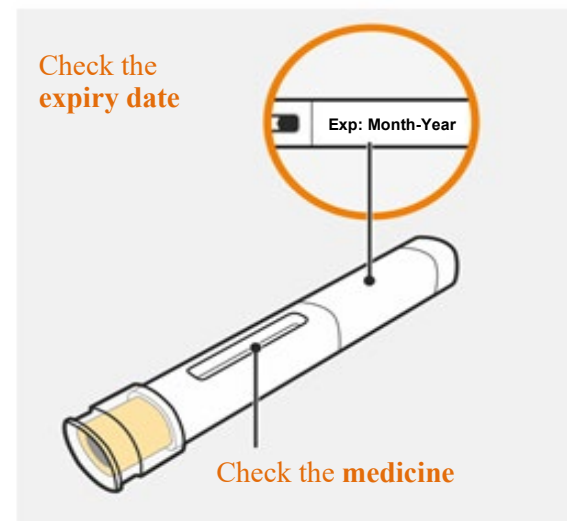


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the pen, carefully take it out of the tray.
- Place the pen on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the pen if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the pen.

- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.

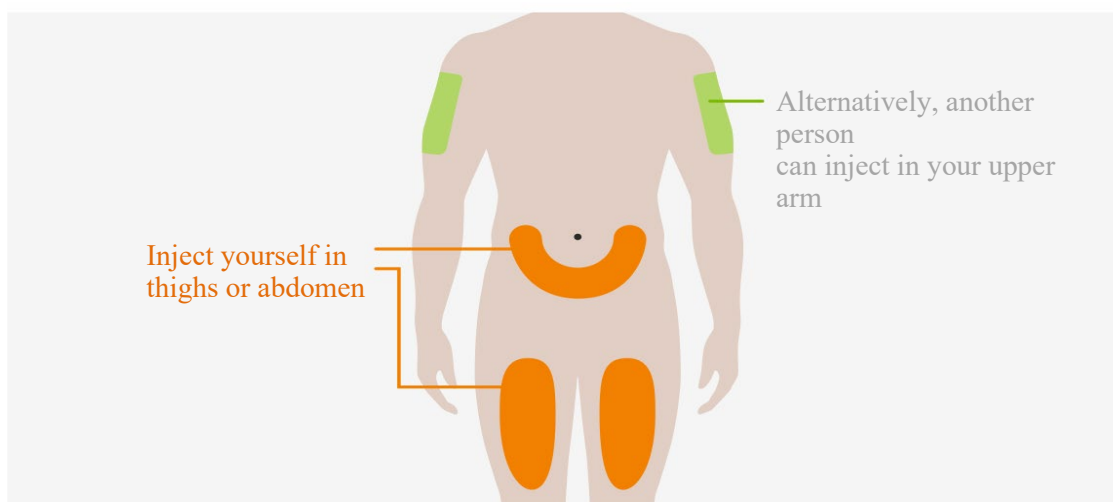
Do not warm the pen in a microwave, hot water, or direct sunlight.

Do not inject if the solution looks cloudy or discoloured, or has particles.

Do not use the pen if left out of the carton for more than 8 hours.

Do not remove the needle cap during this step.

4. Choose your injection site

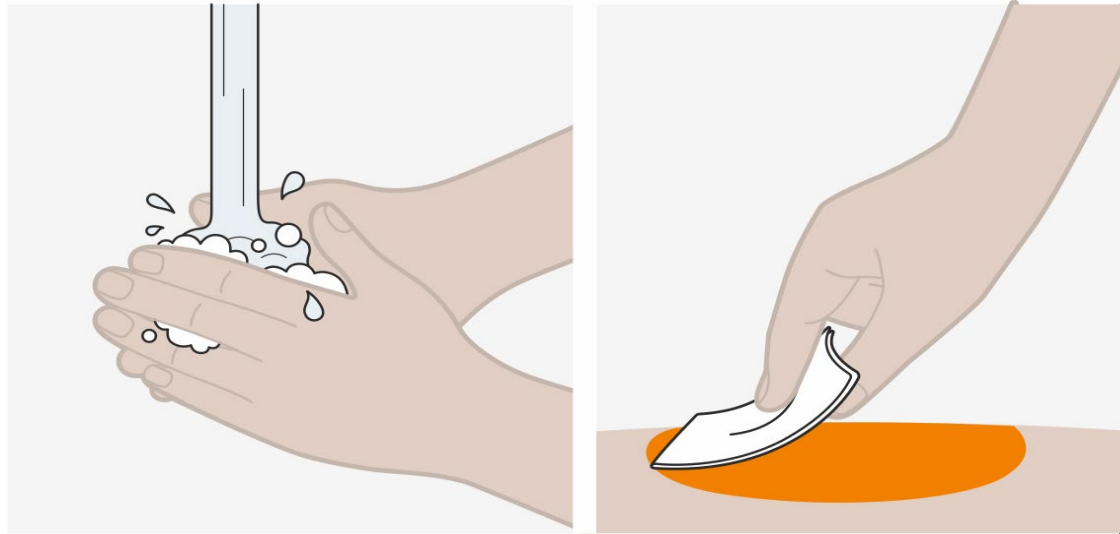


- You can inject Nucala into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.

Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

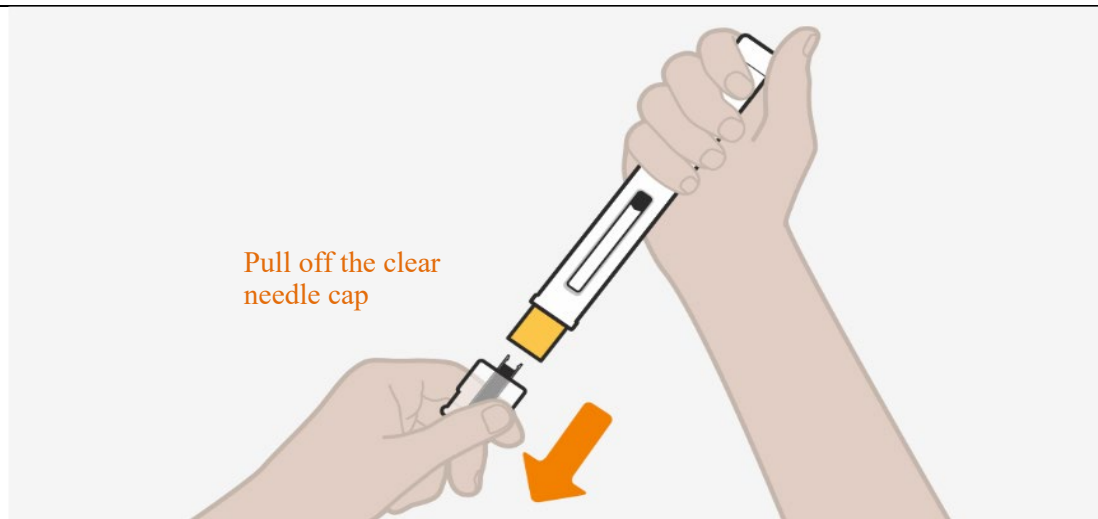


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the clear needle cap

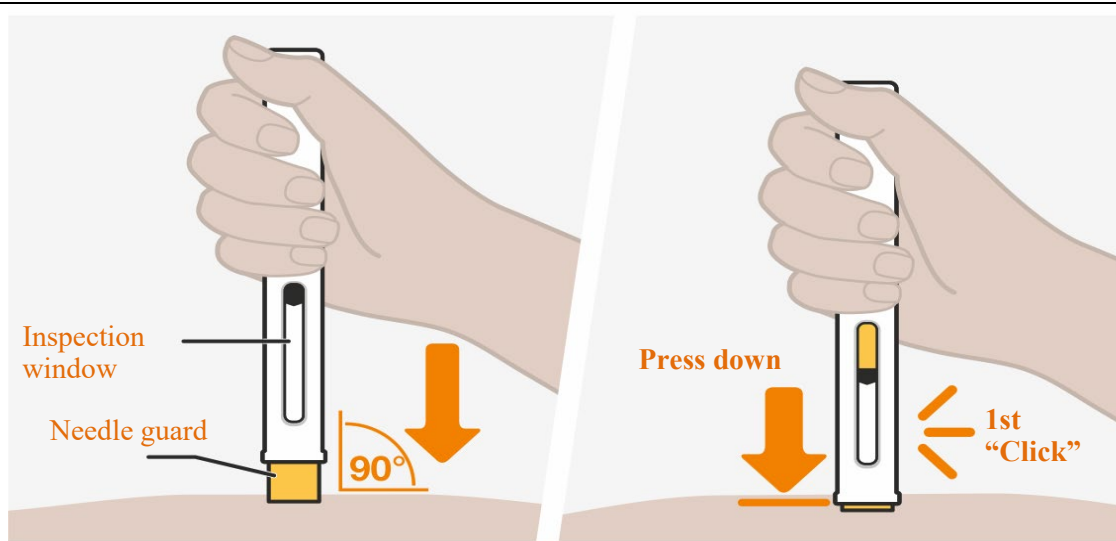


- Remove the clear needle cap from the pen by firmly pulling it straight off.
- Do not worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not touch the yellow needle guard with your fingers. This could activate the pen too soon and may cause a needle injury.

After removal, **do not** put the needle cap back onto the pen, as it may accidentally start the injection.

7. Start your injection

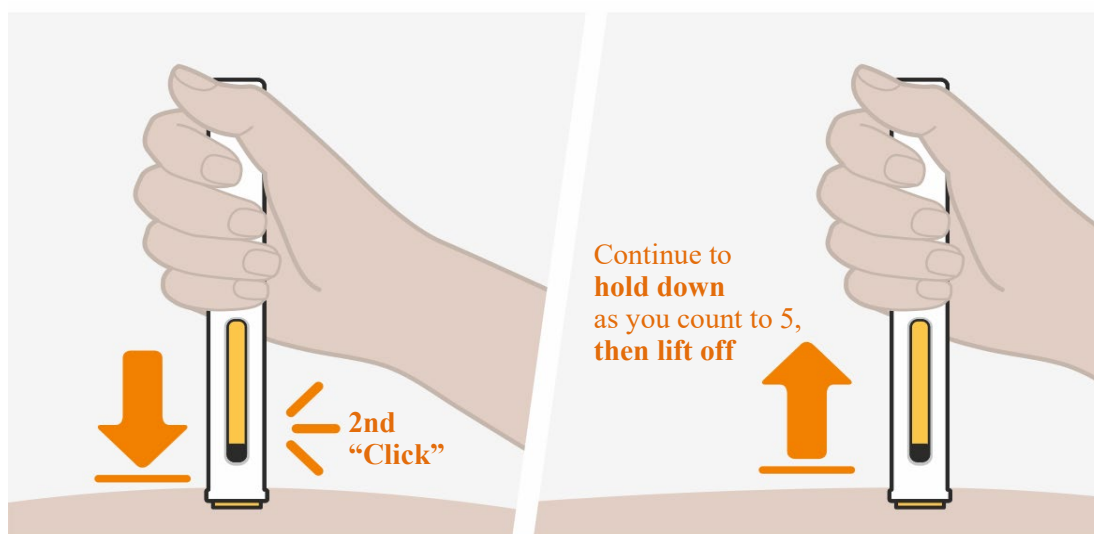


- Hold the pen with its inspection window facing towards you, so you can see it, and with the yellow needle guard facing down.
- Place the pen straight onto your injection site with the yellow needle guard flat against the surface of your skin, as shown.
- To start your injection, push the pen down all the way and keep it held down against your skin. The yellow needle guard will slide up into the pen.
- You should hear the 1st “click” to tell you your injection has started.
- The yellow indicator will move down through the inspection window as you receive your dose.

Do not lift the pen from your skin at this stage, as that may mean you don’t get your full dose of medicine. Your injection may take up to 15 seconds to complete.

Do not use the pen if the yellow needle guard doesn’t slide up as described. Dispose of it (see Step 9), and start again with a new pen.

8. Hold the pen in place to complete your injection



- Continue to hold the pen down until you hear the 2nd “click”, and the stopper and yellow indicator have stopped moving and fill the inspection window.
- Continue to hold the pen in place while you count to 5. Then lift the pen away from your skin.
- If you do **not** hear the 2nd “click”:
 - Check that the inspection window is filled with the yellow indicator.
 - If you are not sure, hold the pen down for another 15 seconds to make sure the injection is complete.

Do not lift the pen until you are sure you have completed your injection.

- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.

Do not rub your injection site.

Dispose

9. Dispose of the used pen

- Dispose of the used pen and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used pens and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 100 mg solution for injection in pre-filled syringe

mepolizumab

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
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

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** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

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

Severe eosinophilic asthma

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.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood, and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps.

Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hyper eosinophilic syndrome (HES)

Hyper eosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of white blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin.

Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids*, Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

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 and adolescents

Severe eosinophilic asthma

The pre-filled syringe is not intended for use in **children below 12 years of age** for the treatment of severe eosinophilic asthma.

For children aged 6-11 years, contact your doctor who will prescribe the recommended dose of Nucala which will be administered by a nurse or doctor.

CRSwNP

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP.

EGPA

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

HES

This medicine is not intended for use in **adolescents or children below 18 years of age** for the treatment of HES.

Other medicines and Nucala

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

Other medicines for asthma, CRSwNP, EGPA or HES

- ✗ **Don't suddenly stop taking** your existing medicines for your asthma, CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent 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.

Nucala contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you or your caregiver can inject Nucala. If appropriate, they will then provide training to show you or your caregiver the correct way to use Nucala.

Nucala must be given to children aged 6 to 11 years by a doctor, nurse or trained caregiver.

Severe eosinophilic asthma

The recommended dose for adults and adolescents aged 12 years and older is 100 mg. You will have 1 injection every four weeks.

CRSwNP

The recommended dose for adults is 100 mg. You will have 1 injection every four weeks.

EGPA

The recommended dose for adults and adolescents aged 12 years and older is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:

The recommended dose is 200 mg. You will have 2 injections every four weeks.

Children weighing less than 40 kg:

The recommended dose is 100 mg. You will have 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

The recommended dose for adults is 300 mg. You will have 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

Instructions for using the pre-filled syringe are given on the other side of this leaflet.

If you use more Nucala than you should

If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed

You or your caregiver should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time for your next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala

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

If your 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 may have had a similar reaction to any injection or medicine:

→ **Tell your doctor** before you (or your child) are given Nucala

Other side effects include:

Very common:

may affect more than 1 in 10 people

- headache

Common:

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 urine, 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
- arthralgia (joint pain)
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Uncommon:

may affect up to 1 in 100 people

- herpes zoster (shingles)

Rare:

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 in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

The Nucala pre-filled syringe can be removed from the refrigerator and kept in its 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.

6. Contents of the pack and other information

What Nucala contains

The active substance is mepolizumab.

Each 1 mL pre-filled syringe contains 100 mg of mepolizumab.

The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 1 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled syringe.

Nucala is available in a pack containing 1 pre-filled syringe or in multipacks comprised of 3 x 1 pre-filled syringes or 9 x 1 pre-filled syringes.

Marketing Authorisation Holder

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, No 90
43056 San Polo di Torrile, Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0) 10 85 52 00

Lietuva

UAB "BERLIN-CHEMIE MENARINI BALTIC"
Tel: + 370 52 691 947
lt@berlin-chemie.com

България

"Берлин-Хеми/А. Менарини
България" ЕООД
Тел.: + 359 2 454 0950
bcsofia@berlin-chemie.com

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Česká republika

GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Magyarország

Berlin-Chemie/A. Menarini Kft.
Tel.: + 36 23501301
bc-hu@berlin-chemie.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Malta

GlaxoSmithKline Trading Services Ltd.
Tel: + 356 80065004

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Eesti

OÜ Berlin-Chemie Menarini Eesti
Tel: + 372 667 5001
ee@berlin-chemie.com

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Ελλάδα

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε.
Τηλ: + 30 210 68 82 100

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

España

GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0)1 39 17 84 44
diam@gsk.com

Portugal

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

Hrvatska

Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: +385 1 4821 361

România

GlaxoSmithKline Trading Services Ltd.
Tel: + 40 800672524

office-croatia@berlin-chemie.com

Ireland

GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Slovenija

Berlin-Chemie / A. Menarini Distribution
Ljubljana d.o.o.
Tel: + 386 (0)1 300 2160
slovenia@berlin-chemie.com

Ísland

Vistor hf.
Sími: + 354 535 7000

Slovenská republika

Berlin-Chemie / A. Menarini Distribution
Slovakia s.r.o.
Tel: + 421 2 544 30 730
slovakia@berlin-chemie.com

Italia

GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Κύπρος

GlaxoSmithKline Trading Services Ltd.
Τηλ: + 357 80070017

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

Latvija

SIA Berlin-Chemie/Menarini Baltic
Tel: + 371 67103210
lv@berlin-chemie.com

United Kingdom (Northern Ireland)

GlaxoSmithKline Trading Services Ltd.
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

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

7. Step by step instructions for using the 100 mg pre-filled syringe

Administer once every four weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. Nucala pre-filled syringe is for use **under the skin only** (subcutaneous).

How to store Nucala

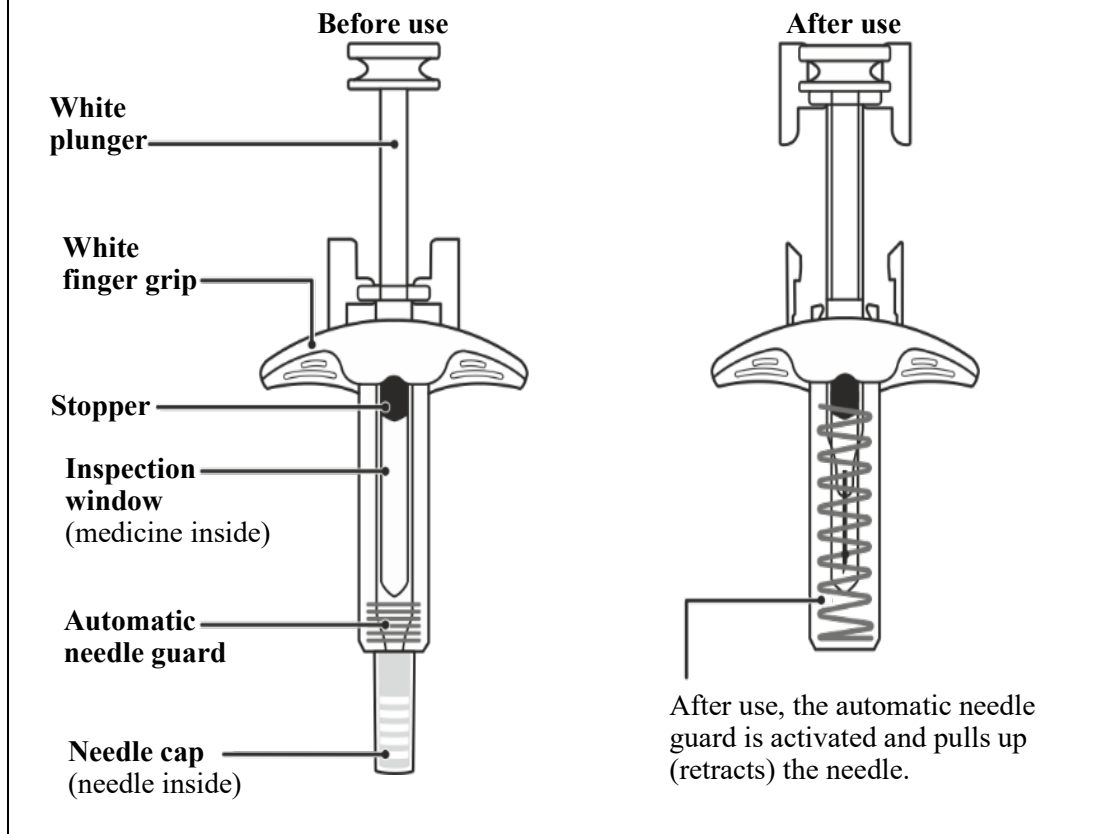
- Keep refrigerated before use.
- Do not freeze.
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled syringe away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use Nucala

The pre-filled syringe should be used only once and then discarded.

- **Do not** share your Nucala pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled syringe



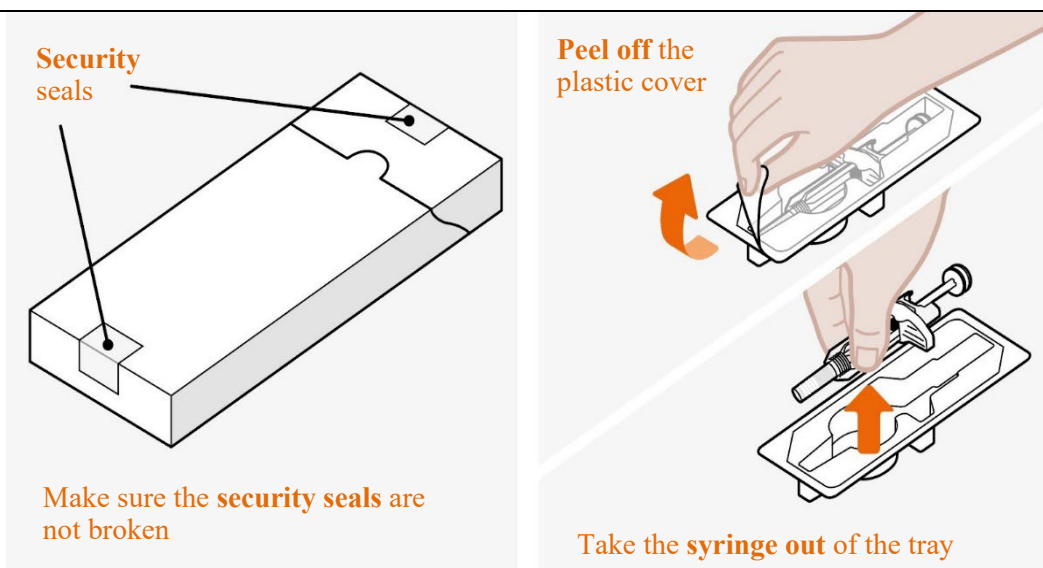
Prepare

1. Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled syringe
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

2. Take out your pre-filled syringe

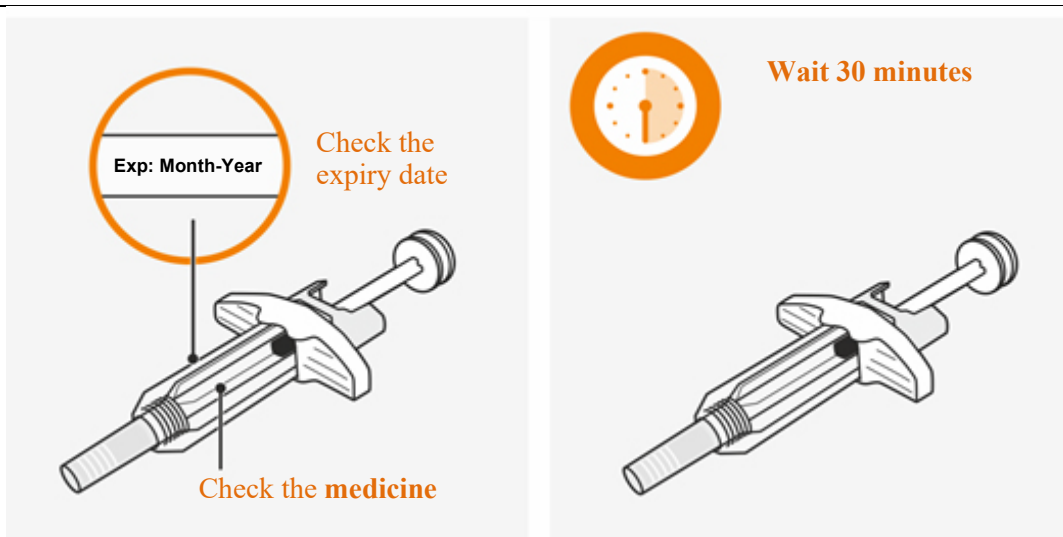


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.

- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.

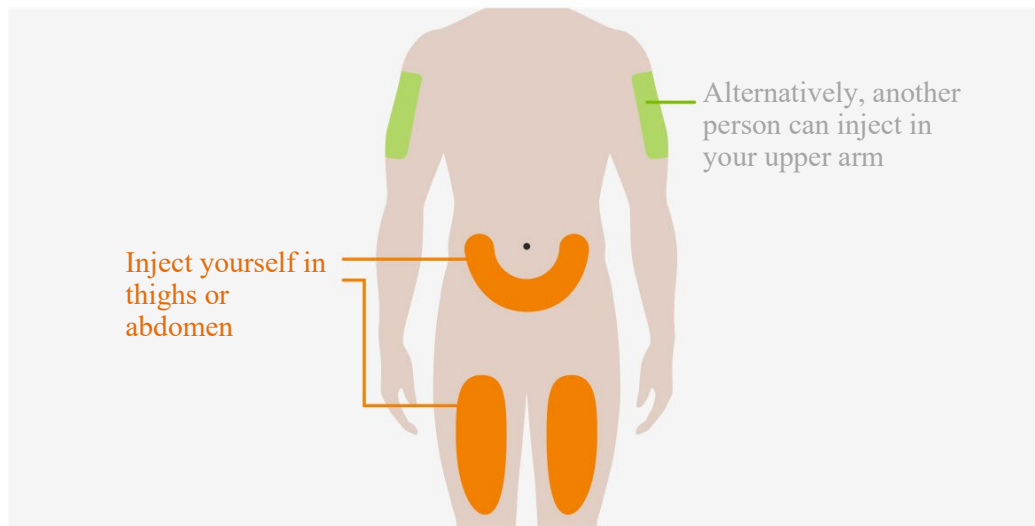
Do not warm the syringe in a microwave, hot water, or direct sunlight.

Do not inject if the solution looks cloudy or discoloured, or has particles.

Do not use the syringe if left out of the carton for more than 8 hours.

Do not remove the needle cap during this step

4. Choose your injection site

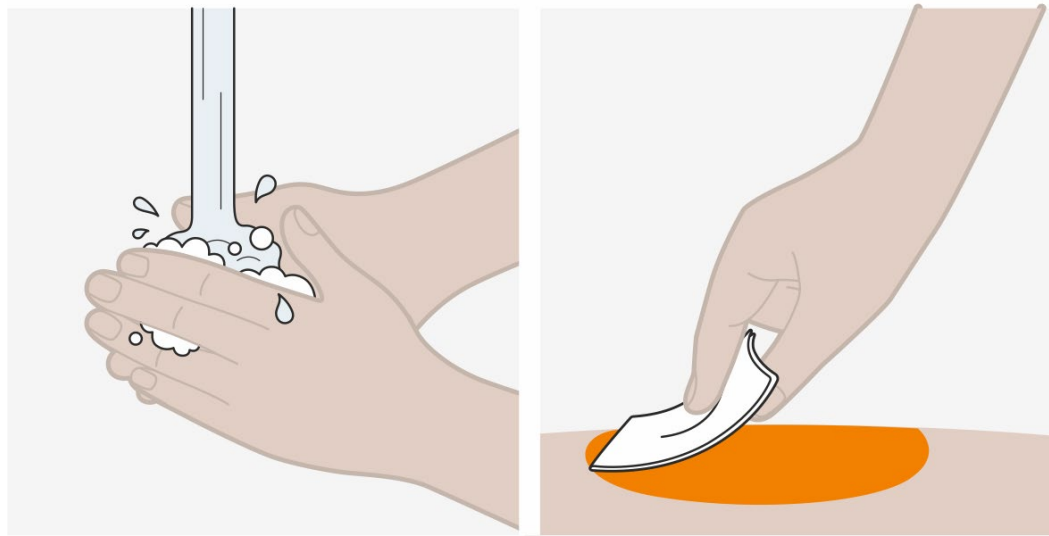


- You can inject Nucala into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose, then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.

Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site



- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not let the needle touch any surface.

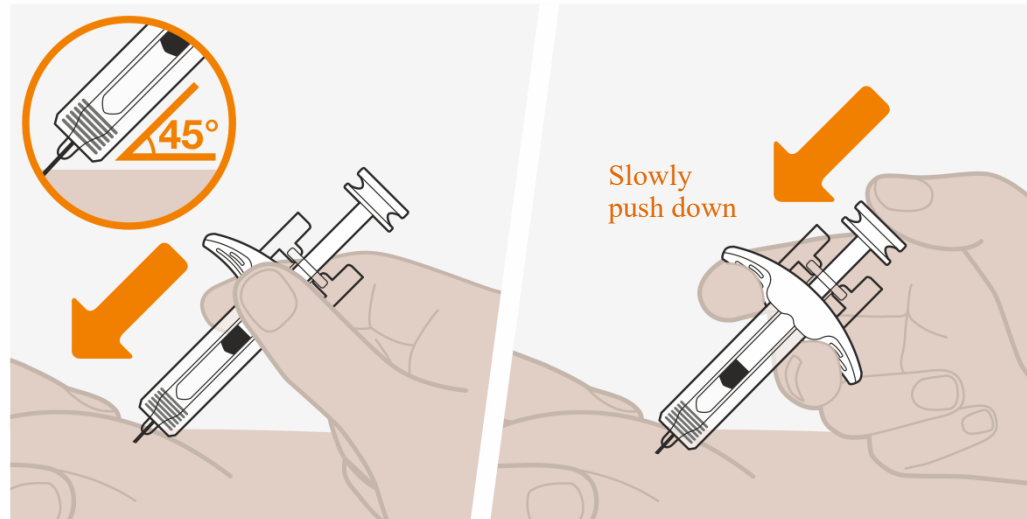
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not receive your full dose.

Do not expel any air bubbles from the syringe.

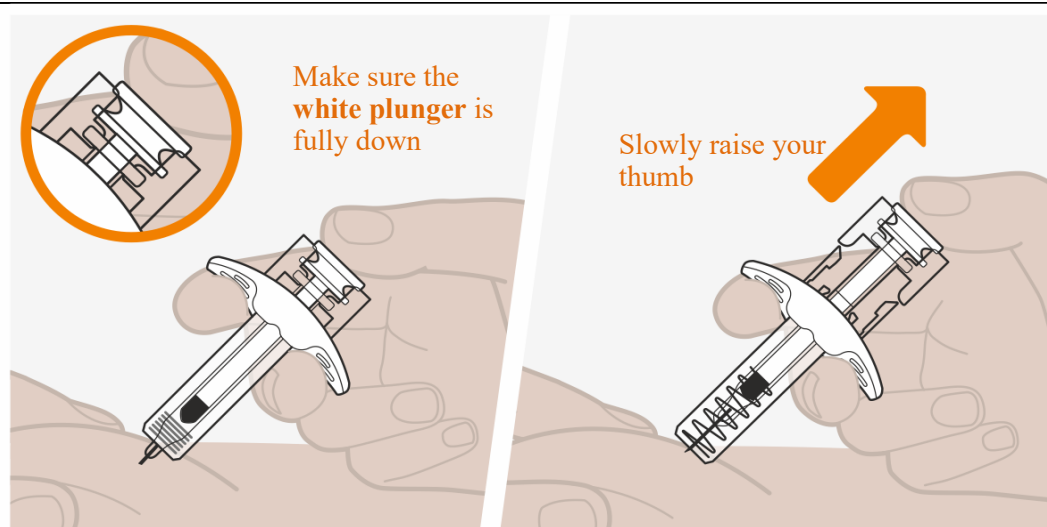
Do not put the needle cap back onto the syringe. This could cause a needle injury.

7. Start your injection



- Use your free hand to pinch the skin around your injection site. Keep the skin pinched throughout your injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject your full dose.

8. Complete your injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub your injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep your used syringes and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 40 mg solution for injection in pre-filled syringe

mepolizumab

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.
- This medicine has been prescribed for a child in your care. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of the child you are caring for.
- If the child gets 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
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

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 years and older.

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 the number of asthma attacks, if the child is already using medicines such as high dose inhalers, but their asthma is not well controlled by these medicines.

If the child is taking medicines called *oral corticosteroids*, Nucala can also help reduce the daily dose they need to control their 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 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 the child you are caring for is **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 the child.

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 the child's asthma remains uncontrolled, or gets worse, after starting 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 the child may have had a similar reaction to any injection or medicine:

→ **Tell your doctor** before you give Nucala.

Parasitic infections

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

→ **Check with your doctor** if you think any of these may apply to the child.

Children and adolescents

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

Other medicines and Nucala

Tell your doctor if the child is taking, has recently taken or might take any other medicines.

Other medicines for asthma

✗ **Don't suddenly stop giving** the child's preventer medicines for their asthma once they have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent on their response to Nucala.

Pregnancy and breast-feeding

Patients who are pregnant, think they may be pregnant or are planning to have a baby, must **ask their doctor for advice** before using this medicine.

It is not known whether the ingredients of Nucala can pass into breast milk. **Patients who are breast-feeding must check with their doctor** before using Nucala.

Driving and using machines

The possible side effects of Nucala are unlikely to affect the ability to drive or use machines.

Nucala contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 40 mg dose, i.e., that is to say essentially "sodium-free".

3. How to use Nucala

Nucala is given by injection just under the skin (*subcutaneous injection*).

Your doctor or nurse will decide if you can inject Nucala for the child you are caring for. If appropriate, they will then provide training to show you the correct way to use Nucala.

The recommended dose for children aged 6 to 11 years old is 40 mg. You will give 1 injection every four weeks.

Instructions for using the pre-filled syringe are given on the other side of this leaflet.

If you use more Nucala than you should

If you think you have injected too much Nucala, **contact your doctor** for advice.

If a dose of Nucala is missed

You should inject the next dose of Nucala as soon as you remember. If you do not notice that you have missed a dose until it is already time to give the next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Stopping treatment with Nucala

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

If the child's 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 the child may be having a reaction.

If the child may have had a similar reaction to any injection or medicine:

→ **Tell your doctor** before the child is given Nucala

Other side effects include:

Very common:

may affect more than 1 in 10 people

- headache

Common:

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 urine, 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
- arthralgia (joint pain)
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Uncommon:

may affect up to 1 in 100 people

- herpes zoster (shingles)

Rare:

may affect up to 1 in 1 000 people

- Severe allergic reactions (*anaphylaxis*)

→ **Tell your doctor or a nurse immediately** if the child gets 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 in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

The Nucala pre-filled syringe can be removed from the refrigerator and kept in its 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.

6. Contents of the pack and other information

What Nucala contains

The active substance is mepolizumab.

Each 0.4 mL pre-filled syringe contains 40 mg of mepolizumab.

The other ingredients are sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections.

What Nucala looks like and contents of the pack

Nucala is supplied as a 0.4 mL clear to opalescent, colourless to pale yellow to pale brown solution in a single use pre-filled syringe.

Nucala is available in a pack containing 1 pre-filled syringe or in multipacks comprised of 3 x 1 pre-filled syringes.

Marketing Authorisation Holder

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer

GlaxoSmithKline Manufacturing S.P.A
Strada Provinciale Asolana, No 90
43056 San Polo di Torrile, Parma
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0) 10 85 52 00

Lietuva

UAB "BERLIN-CHEMIE MENARINI BALTIC"
Tel: + 370 52 691 947
lt@berlin-chemie.com

България

"Берлин-Хеми/А. Менарини
България" ЕООД
Тел.: + 359 2 454 0950
bcsofia@berlin-chemie.com

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Česká republika

GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Magyarország

Berlin-Chemie/A. Menarini Kft.
Tel.: + 36 23501301
bc-hu@berlin-chemie.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Malta

GlaxoSmithKline Trading Services Ltd.
Tel: + 356 80065004

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti

OÜ Berlin-Chemie Menarini Eesti
Tel: + 372 667 5001
ee@berlin-chemie.com

Ελλάδα

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε.
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska

Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: +385 1 4821 361
office-croatia@berlin-chemie.com

Ireland

GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland

Vistor hf.
Sími: + 354 535 7000

Italia

GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 7741111

Κύπρος

GlaxoSmithKline Trading Services Ltd.
Τηλ: + 357 80070017

Latvija**Nederland**

GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline Trading Services Ltd.
Tel: + 40 800672524

Slovenija

Berlin-Chemie / A. Menarini Distribution
Ljubljana d.o.o.
Tel: + 386 (0)1 300 2160
slovenia@berlin-chemie.com

Slovenská republika

Berlin-Chemie / A. Menarini Distribution
Slovakia s.r.o.
Tel: + 421 2 544 30 730
slovakia@berlin-chemie.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom (Northern Ireland)

SIA Berlin-Chemie/Menarini Baltic
Tel: + 371 67103210
lv@berlin-chemie.com

GlaxoSmithKline Trading Services Ltd.
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

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

7. Step by step instructions for using the 40 mg pre-filled syringe

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. Nucala pre-filled syringe is for **use under the skin only** (subcutaneous).

How to store Nucala

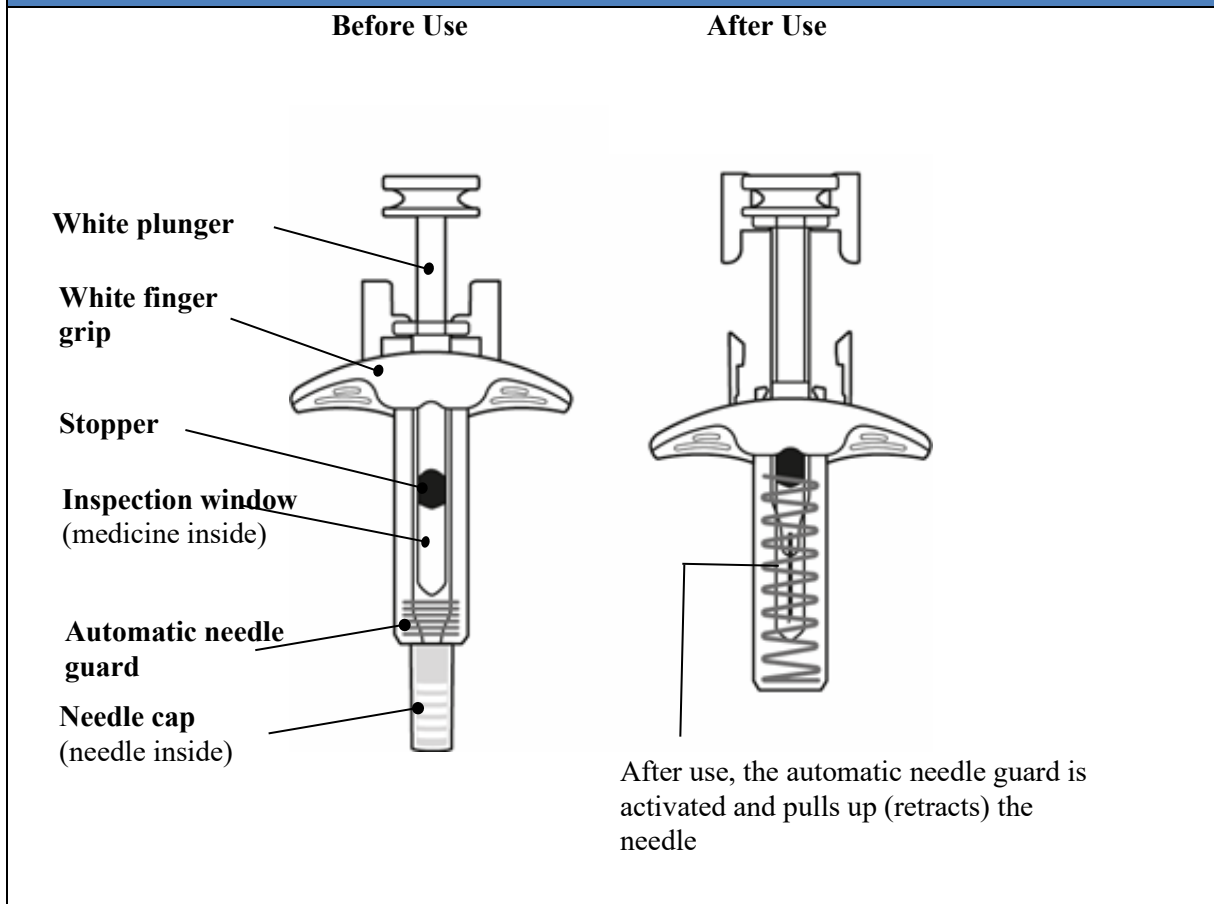
- Keep refrigerated before use.
- Do not freeze
- Keep the pre-filled syringe in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton. Safely, throw the pre-filled syringe away if it has been kept out of the refrigerator for more than 7 days.
- Do not store it above 30°C.

Before you use Nucala

The pre-filled syringe should be used only once and then discarded.

- **Do not** share the Nucala pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before the injection.

Know the pre-filled syringe



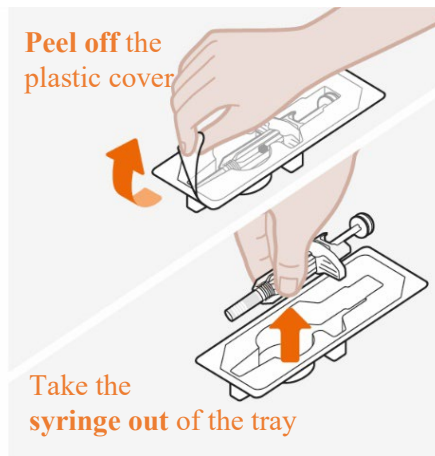
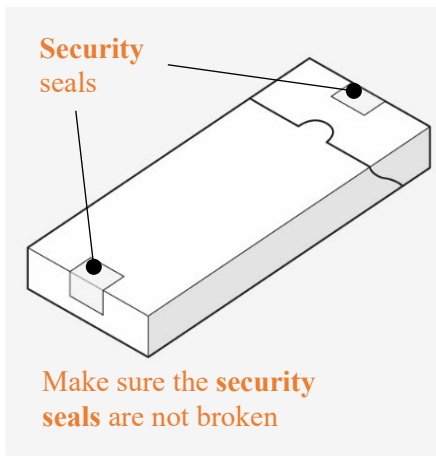
Prepare

1. Get ready what you need

Find a comfortable, well-lit and clean surface. Make sure you have within reach:

- Nucala pre-filled syringe
- Alcohol wipe (not included)
- Gauze pad or cotton wool ball (not included)

2. Take out the pre-filled syringe

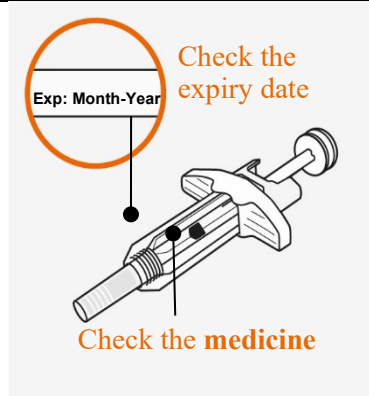


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the syringe.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.

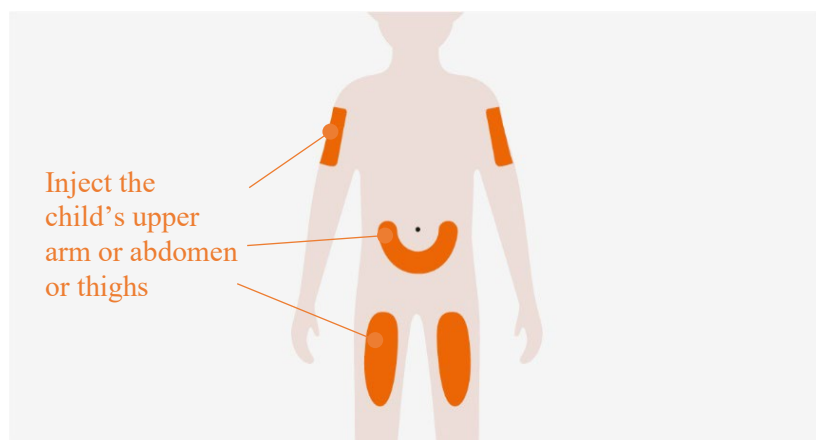
Do not warm the syringe in a microwave, hot water, or direct sunlight.

Do not inject if the solution looks cloudy or discoloured, or has particles.

Do not use the syringe if left out of the carton for more than 8 hours.

Do not remove the needle cap during this step.

4. Choose the injection site

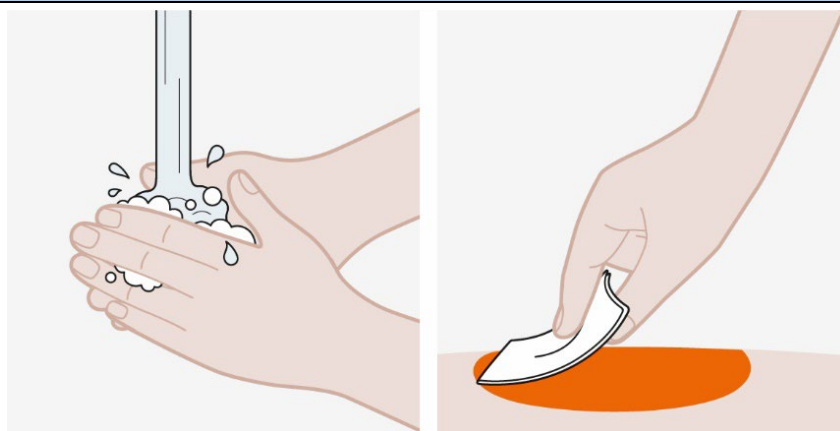


- You can inject Nucala into the upper arm, abdomen or thigh of the child you are caring for.

Do not inject where the skin is bruised, tender, red or hard.

Do not inject within 5 cm of the navel (belly button).

5. Clean the injection site



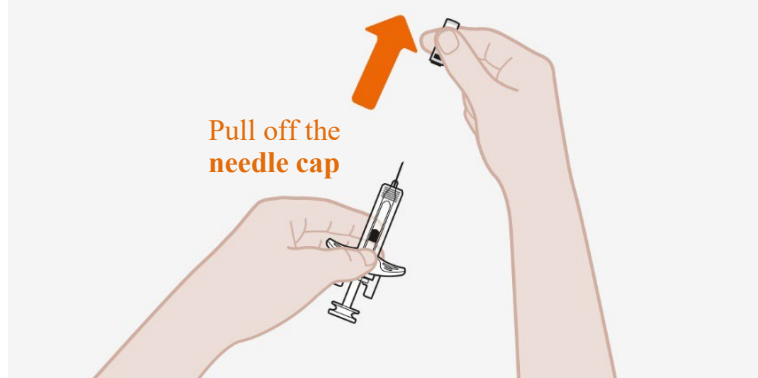
- Wash your hands with soap and water.

- Clean the injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch the cleaned injection site again until you have finished the injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and **always** within 5 minutes.

Do not let the needle touch any surface.

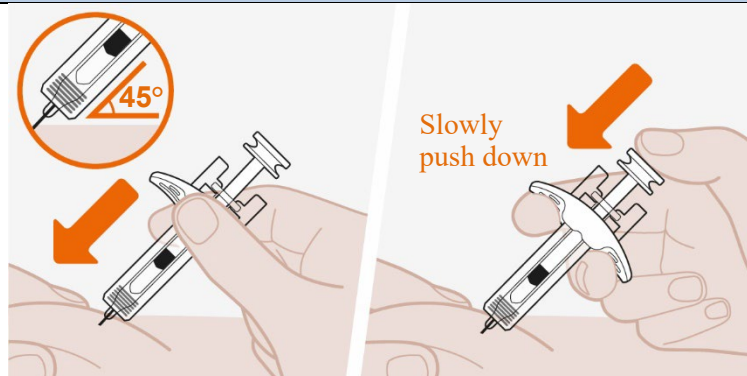
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not give the full dose.

Do not expel any air bubbles from the syringe.

Do not put the needle cap back onto the syringe. This could cause a needle injury.

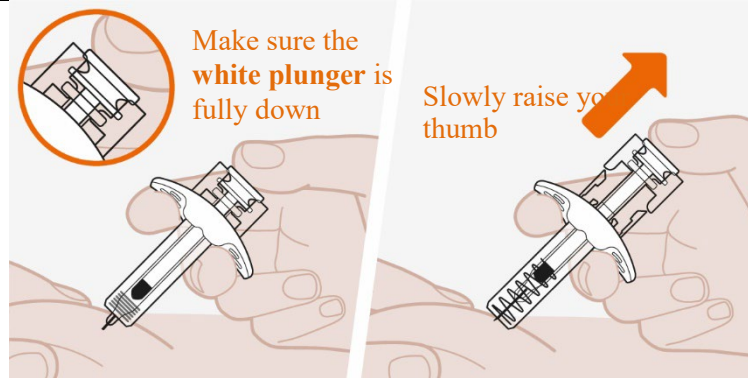
7. Start the injection



- Use your free hand to pinch the skin around the injection site. Keep the skin pinched throughout the injection.

- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject the full dose.

8. Complete the injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub the injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- **Keep the used syringes and needle caps out of the sight and reach of children.**

Package leaflet: Information for the user

Nucala 100 mg powder for solution for injection mepolizumab

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
2. What you need to know before you use Nucala
3. How to use Nucala
4. Possible side effects
5. How to store Nucala
6. Contents of the pack and other information
7. Step-by-step instructions for use

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** and **EGPA** (Eosinophilic Granulomatosis with Polyangiitis) in adults, adolescents and children aged 6 years and older. It is also used to treat **CRSwNP** (Chronic Rhinosinusitis with Nasal Polyps) and **HES** (Hypereosinophilic syndrome) in adults.

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

Severe eosinophilic asthma

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.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

CRSwNP is a condition in which people have too many *eosinophils* (a type of white blood cell) in the blood and tissue lining the nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

Nucala reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevent surgery for nasal polyps. Nucala can also help reduce the need for *oral corticosteroids* to control your symptoms.

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is a condition where people have too many *eosinophils* (a type of white blood cell) in the blood and tissues and also have a form of *vasculitis*. This means there is inflammation of the blood vessels. This condition most commonly affects the lungs and sinuses but often affects other organs such as the skin, heart and kidneys.

Nucala can control and delay a flare-up of these EGPA symptoms. This medicine can also help reduce the daily dose of *oral corticosteroids* you need to control your symptoms.

Hypereosinophilic syndrome (HES)

Hypereosinophilic syndrome (HES) is a condition in which there are a high number of *eosinophils* (a type of white blood cell) in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves and skin.

Nucala helps reduce your symptoms and prevents flares. If you are taking medicines often referred to as *oral corticosteroids*, Nucala can also help reduce the daily dose you need to control your HES symptoms/flares.

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

Severe eosinophilic asthma and EGPA

This medicine is not intended for use in **children below 6 years of age** for the treatment of severe eosinophilic asthma or EGPA.

CRSwNP and HES

This medicine is not intended for use in **children or adolescents below 18 years of age** for the treatment of CRSwNP or HES.

Other medicines and Nucala

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

Other medicines for asthma, CRSwNP, EGPA or HES

- ✗ **Don't suddenly stop taking** your existing medicines for your asthma, CRSwNP, EGPA or HES once you have started Nucala. These medicines (especially ones called *oral corticosteroids*) must be stopped gradually, under the direct supervision of your doctor and dependent 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.

Nucala contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e., that is to say essentially "sodium-free".

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).

Severe eosinophilic asthma

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.

CRSwNP

Adults

The recommended dose for adults is 100 mg. You will be given 1 injection every four weeks.

EGPA

Adults and adolescents aged 12 years and over

The recommended dose for adults and adolescents is 300 mg. You will have 3 injections every four weeks.

Children aged 6 to 11 years old

Children weighing 40 kg or more:

The recommended dose is 200 mg. You will be given 2 injections every four weeks.

Children weighing less than 40 kg:

The recommended dose is 100 mg. You will be given 1 injection every four weeks.

The injection sites should be at least 5 cm apart.

HES

Adults

The recommended dose for adults is 300 mg. You will be given 3 injections every four weeks.

The injection sites should be at least 5 cm apart.

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 symptoms and attacks to come back.

If your 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:

may affect more than 1 in 10 people

- headache

Common:

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 urine, 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
- arthralgia (joint pain)
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Uncommon:

may affect up to 1 in 100 people

- herpes zoster (shingles)

Rare:

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.

Marketing Authorisation Holder

GlaxoSmithKline Trading Services Limited

12 Riverwalk

Citywest Business Campus

Dublin 24

Ireland

Manufacturer

GlaxoSmithKline Manufacturing S.P.A

Strada Provinciale Asolana, No 90

43056 San Polo di Torrile, Parma

Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals s.a./n.v.

Tél/Tel: + 32 (0) 10 85 52 00

Lietuva

UAB "BERLIN-CHEMIE MENARINI BALTIC"

Tel: + 370 52 691 947

lt@berlin-chemie.com

България

"Берлин-Хеми/А. Менарини

България" ЕООД

Тел.: + 359 2 454 0950

bcsafia@berlin-chemie.com

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals s.a./n.v.

Belgique/Belgien

Tél/Tel: + 32 (0) 10 85 52 00

Česká republika

GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf.: + 45 36 35 91 00
dk-info@gsk.com

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti

OÜ Berlin-Chemie Menarini Eesti
Tel: + 372 667 5001
ee@berlin-chemie.com

Ελλάδα

GlaxoSmithKline Μονοπρόσωπη Α.Ε.Β.Ε.
Τηλ: + 30 210 68 82 100

España

GlaxoSmithKline, S.A.
Tel: + 34 900 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska

Berlin-Chemie Menarini Hrvatska d.o.o.
Tel: +385 1 4821 361
office-croatia@berlin-chemie.com

Ireland

GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland

Vistor hf.
Sími: + 354 535 7000

Italia

GlaxoSmithKline S.p.A.

Magyarország

Berlin-Chemie/A. Menarini Kft.
Tel.: + 36 23501301
bc-hu@berlin-chemie.com

Malta

GlaxoSmithKline Trading Services Ltd.
Tel: + 356 80065004

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)33 2081100

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline Trading Services Ltd.
Tel: + 40 800672524

Slovenija

Berlin-Chemie / A. Menarini Distribution
Ljubljana d.o.o.
Tel: + 386 (0)1 300 2160
slovenia@berlin-chemie.com

Slovenská republika

Berlin-Chemie / A. Menarini Distribution
Slovakia s.r.o.
Tel: + 421 2 544 30 730
slovakia@berlin-chemie.com

Suomi/Finland

GlaxoSmithKline Oy

Tel: + 39 (0)45 7741111

Puh/Tel: + 358 (0)10 30 30 30

Κύπρος

GlaxoSmithKline Trading Services Ltd.

Τηλ: + 357 80070017

Sverige

GlaxoSmithKline AB

Tel: + 46 (0)8 638 93 00

info.produkt@gsk.com

Latvija

SIA Berlin-Chemie/Menarini Baltic

Tel: + 371 67103210

lv@berlin-chemie.com

United Kingdom (Northern Ireland)

GlaxoSmithKline Trading Services Ltd.

Tel: + 44 (0)800 221441

customercontactuk@gsk.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<https://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

7. 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. 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.

Traceability

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

Instructions for reconstitution for each vial

1. **Reconstitute the contents of the vial with 1.2 mL of sterile water for injections** preferably using a 2 to 3 ml syringe and a 21 gauge needle. The 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 1 000 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 from one vial. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

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

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.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for mepolizumab, the scientific conclusions of PRAC are as follows:

In view of available data on herpes zoster and arthralgia from clinical trials, the literature and spontaneous cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between mepolizumab and herpes zoster and between mepolizumab and arthralgia is at least a reasonable possibility. The PRAC concluded that the product information of products containing mepolizumab should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for mepolizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing mepolizumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.