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

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.

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

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

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

4.2 **Posology and method of administration**

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

**Posology**

*Adults and adolescents aged 12 years and over*

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 considered at least on an annual basis as determined by physician assessment of the patient’s disease severity and level of control of exacerbations.

**Special populations**

*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

Children aged 6 to 11 years old
Nucala 100 mg solution for injection in pre-filled pen and Nucala 100 mg solution for injection in pre-filled syringe are not indicated for administration to this population.

The powder for solution for injection presentation is appropriate for administration to this population. The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

Children less than 6 years old
The safety and efficacy of mepolizumab in children less than 6 years old have not yet been established.
No data are available.

Method of administration

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

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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

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

Corticosteroids

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

**Hypersensitivity and administration-related reactions**

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

**Parasitic infections**

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

**Excipients**

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

**4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women. Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.

As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy. Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

**Breast-feeding**

There are no data regarding the excretion of mepolizumab in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys at concentrations of less than 0.5% of those detected in plasma.
A decision must be made whether to discontinue breast-feeding or to discontinue Nucala therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**Fertility**

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

#### Summary of the safety profile

**Adults and adolescents**

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

#### Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled studies with frequencies from subjects receiving mepolizumab 100 mg SC (n= 263), and from spontaneous post-marketing reports. Safety data is 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 frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Lower respiratory tract infection</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions (systemic allergic)*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis**</td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Very common</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain upper</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Eczema</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Administration-related reactions (systemic non allergic)**</td>
<td>Common</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse reactions</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Local injection site reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td></td>
</tr>
</tbody>
</table>

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

**From spontaneous post marketing reporting.

*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reaction

**Local injection site reactions**

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

**Paediatric population**

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.

**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**

In patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/μL at week 32 (n=182), a reduction of 84% compared to placebo. This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.

In adults, adolescents and children, this magnitude of reduction was observed within 4 weeks of treatment.

**Immunogenicity**

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents treated with 100 mg dose subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.

The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) 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 subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

**Clinical efficacy**

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance
treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting 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 1192 patients, 60% females, with a mean age of 49 years (range 12–82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator 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 medicine during the studies.

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

**Dose-ranging efficacy MEA112997 (DREAM) study**

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

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

<table>
<thead>
<tr>
<th></th>
<th>Intravenous mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75mg n=153</td>
<td>250mg n=152</td>
</tr>
<tr>
<td>Exacerbation rate/year</td>
<td>1.24</td>
<td>1.46</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>48%</td>
<td>39%</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.52 (0.39, 0.69)</td>
<td>0.61(0.46, 0.81)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Exacerbation reduction MEA115588 (MENSA) study**

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

Patients received mepolizumab 100 mg administered subcutaneously, mepolizumab 75 mg administered intravenously or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint was the frequency of clinically significant exacerbations of asthma and the reductions for both mepolizumab treatment arms compared to placebo were statistically significant (p<0.001). Table 2 provides the results of the primary and secondary endpoints for patients treated with subcutaneous mepolizumab or placebo.
Table 2: Results of primary and secondary endpoints at week 32 in the intent to treat population (MEA115588)

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab 100 mg (subcutaneous) N= 194</th>
<th>Placebo N= 191</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of clinically significant exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>0.83</td>
<td>1.74</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>53%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.47 (0.35, 0.64)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of exacerbations requiring hospitalisations/emergency room visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>61%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.39 (0.18, 0.83)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.015</td>
<td>-</td>
</tr>
<tr>
<td>Frequency of exacerbations requiring hospitalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations rate per year</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>69%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.31 (0.11, 0.91)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.034</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pre-bronchodilator FEV₁ (mL) at week 32</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>1730 (659)</td>
<td>1860 (631)</td>
</tr>
<tr>
<td>Mean change from baseline (SE)</td>
<td>183 (31)</td>
<td>86 (31)</td>
</tr>
<tr>
<td>Difference (mepolizumab vs. placebo)</td>
<td>98</td>
<td>-</td>
</tr>
<tr>
<td>95% CI</td>
<td>(11, 184)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.028</td>
<td>-</td>
</tr>
<tr>
<td><strong>St. George’s Respiratory Questionnaire (SGRQ) at week 32</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>47.9 (19.5)</td>
<td>46.9 (19.8)</td>
</tr>
<tr>
<td>Mean change from baseline (SE)</td>
<td>-16.0 (1.1)</td>
<td>-9.0 (1.2)</td>
</tr>
<tr>
<td>Difference (mepolizumab vs. placebo)</td>
<td>-7.0</td>
<td>-</td>
</tr>
<tr>
<td>95% CI</td>
<td>(-10.2, -3.8)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

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
### Oral corticosteroid reduction study MEA115575 (SIRIUS)

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

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

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

**Table 4: Results of the primary and secondary endpoints in MEA115575**
### ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab (subcutaneous)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 69</td>
<td></td>
<td>N= 66</td>
</tr>
</tbody>
</table>

#### Primary endpoint

**Percent reduction in OCS from baseline (weeks 20-24)**

<table>
<thead>
<tr>
<th>Reduction in OCS from baseline (%)</th>
<th>Mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% - 100%</td>
<td>16 (23%)</td>
<td>7(11%)</td>
</tr>
<tr>
<td>75% - &lt;90%</td>
<td>12 (17%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>50% - &lt;75%</td>
<td>9 (13%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>&gt;0% - &lt;50%</td>
<td>7 (10%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>No decrease in OCS/lack of asthma control/ withdrawal from treatment</td>
<td>25 (36%)</td>
<td>37 (56%)</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI) 2.39 (1.25, 4.56)
p-value 0.008

#### Secondary endpoints (weeks 20-24)

<table>
<thead>
<tr>
<th>Reduction in the daily OCS dose to 0 mg/d</th>
<th>Mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 (14%)</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI) 1.67 (0.49, 5.75)
p-value 0.414

<table>
<thead>
<tr>
<th>Reduction in the daily OCS dose to ≤5mg/day</th>
<th>Mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37 (54%)</td>
<td>21 (32%)</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI) 2.45 (1.12, 5.37)
p-value 0.025

<table>
<thead>
<tr>
<th>Median % reduction in daily OCS dose from baseline (95% CI)</th>
<th>Mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50.0 (20.0, 75.0)</td>
<td>0.0 (-20.0, 33.3)</td>
</tr>
</tbody>
</table>

Median difference (95% CI) -30.0 (-66.7, 0.0)
p-value 0.007

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

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

**Paediatric population**

**Severe refractory eosinophilic asthma**

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

#### 5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. 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 ($T_{\text{max}}$) ranging from 4 to 8 days.

Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

**Distribution**

Following a single intravenous administration to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

**Biotransformation**

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

**Elimination**

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

**Special populations**

*Elderly patients (≥65 years old)*

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

*Renal impairment*

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

*Hepatic impairment*

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

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

Paediatric pharmacokinetics following subcutaneous administration in subjects 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg.
Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

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 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 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 comprising 3 (3 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 comprising 3 (3 packs of 1) pre-filled syringe

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 from the refrigerator, allow the pen or syringe 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 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)

EU/1/15/1043/003 1 pre-filled pen
EU/1/15/1043/004 3 (3 x 1) pre-filled pens (multipack)
EU/1/15/1043/005 1 pre-filled syringe
EU/1/15/1043/006 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 http://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**

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

4.2 **Posology and method of administration**

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

**Posology**

*Adults and adolescents aged 12 years and older*

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

*Children aged 6 to 11 years old*

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

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

**Special populations**

*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

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

Method of administration

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

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

Each vial of 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.

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

Adults and adolescents

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

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled studies with frequencies from subjects receiving mepolizumab 100 mg SC (n=263), and from spontaneous post-marketing reports. Safety data is 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 frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Lower respiratory tract infection</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions (systemic allergic)*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis**</td>
<td>Rare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Very common</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain upper</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Eczema</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Administration-related reactions (systemic non allergic)***</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Local injection site reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td></td>
</tr>
</tbody>
</table>
* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

**From spontaneous post marketing reporting.

*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of subjects receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reaction

Local injection site reactions

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

Paediatric population

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.

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
Mechanism of action

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

In patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/µL at week 32 (n=182), a reduction of 84% compared to placebo.

This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/µL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.

In adults, adolescents and children, this magnitude of reduction was observed within 4 weeks of treatment.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents treated with 100 mg dose subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.

The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) 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 subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Clinical efficacy

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of
care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting 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 1192 patients, 60% females, with a mean age of 49 years (range 12–82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator 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 medicine during the studies.

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

Dose-ranging efficacy MEA112997 (DREAM) study

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

<table>
<thead>
<tr>
<th>Intravenous mepolizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>75mg n=153</td>
<td>250mg n=152</td>
</tr>
<tr>
<td>Exacerbation rate/year</td>
<td>1.24</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>48%</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.52 (0.39, 0.69)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Exacerbation reduction MEA115588 (MENSA) study

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Mepolizumab 100 mg (subcutaneous) N= 194</th>
<th>Placebo N= 191</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of clinically significant exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>0.83</td>
<td>1.74</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>53%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.47 (0.35, 0.64)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of exacerbations requiring hospitalisations/emergency room visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>0.08</td>
<td>0.20</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>61%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.39 (0.18, 0.83)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Frequency of exacerbations requiring hospitalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations rate per year</td>
<td>0.03</td>
<td>0.10</td>
</tr>
<tr>
<td>Percent reduction</td>
<td>69%</td>
<td>-</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.31 (0.11, 0.91)</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.034</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-bronchodilator FEV1 (mL) at week 32</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>1730 (659)</td>
<td>1860 (631)</td>
</tr>
<tr>
<td>Mean change from baseline (SE)</td>
<td>183 (31)</td>
<td>86 (31)</td>
</tr>
<tr>
<td>Difference (mepolizumab vs. placebo)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(11, 184)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td><strong>St. George’s Respiratory Questionnaire (SGRQ) at week 32</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (SD)</td>
<td>47.9 (19.5)</td>
<td>46.9 (19.8)</td>
</tr>
<tr>
<td>Mean change from baseline (SE)</td>
<td>-16.0 (1.1)</td>
<td>-9.0 (1.2)</td>
</tr>
<tr>
<td>Difference (mepolizumab vs. placebo)</td>
<td>-7.0</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(-10.2, -3.8)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Baseline Eosinophil Count</th>
<th>Mepolizumab 75 mg IV/100 mg SC N=538</th>
<th>Placebo N=346</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEA112997+MEA115588 &lt;150 cells/µL</td>
<td>n=123</td>
<td>n=66</td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>1.16</td>
<td>1.73</td>
</tr>
<tr>
<td>Mepolizumab vs. placebo</td>
<td>Rate ratio (95% CI)</td>
<td>0.67 (0.46,0.98)</td>
</tr>
<tr>
<td>150 to &lt;300 cells/µL</td>
<td>n=139</td>
<td>n=86</td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>1.01</td>
<td>1.41</td>
</tr>
<tr>
<td>Mepolizumab vs. placebo</td>
<td>Rate ratio (95% CI)</td>
<td>0.72 (0.47,1.10)</td>
</tr>
<tr>
<td>300 to &lt;500 cells/µL</td>
<td>n=109</td>
<td>n=76</td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>1.02</td>
<td>1.64</td>
</tr>
<tr>
<td>Mepolizumab vs. placebo</td>
<td>Rate ratio (95% CI)</td>
<td>0.62 (0.41,0.93)</td>
</tr>
<tr>
<td>≥500 cells/µL</td>
<td>n=162</td>
<td>n=116</td>
</tr>
<tr>
<td>Exacerbation rate per year</td>
<td>0.67</td>
<td>2.49</td>
</tr>
<tr>
<td>Mepolizumab vs. placebo</td>
<td>Rate ratio (95% CI)</td>
<td>0.27 (0.19,0.37)</td>
</tr>
</tbody>
</table>

Oral corticosteroid reduction study MEA115575 (SIRIUS)

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

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

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

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

**Percent reduction in OCS from baseline (weeks 20-24)**

<table>
<thead>
<tr>
<th>Reduction in OCS from baseline</th>
<th>ITT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% - 100%</td>
<td>Mepolizumab 700 mg (subcutaneous) N= 69</td>
</tr>
<tr>
<td>75% - &lt;90%</td>
<td>16 (23%)</td>
</tr>
<tr>
<td>50% - &lt;75%</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>&gt;0% - &lt;50%</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>No decrease in OCS/lack of asthma control/ withdrawal from treatment</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.39 (1.25, 4.56)</td>
</tr>
<tr>
<td>p-value</td>
<td>008</td>
</tr>
</tbody>
</table>

### Secondary endpoints (weeks 20-24)

- **Reduction in the daily OCS dose to 0 mg/d**
  - Mepolizumab: 10 (14%)  
  - Placebo: 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**
  - Mepolizumab: 37 (54%)  
  - Placebo: 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)**
  - Mepolizumab: 50.0 (20.0, 75.0)  
  - Placebo: 0.0 (-20.0, 33.3)  
  - Median difference (95% CI): -30.0 (-66.7, 0.0)  
  - p-value: 0.007

---

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

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

**Paediatric population**

**Severe refractory eosinophilic asthma**

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

### 5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg.
Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration ($T_{\text{max}}$) ranging from 4 to 8 days. Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single intravenous administration to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

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

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special populations

**Elderly patients (≥65 years old)**

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

**Renal impairment**

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

**Hepatic impairment**

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

**Paediatric population**

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

Paediatric pharmacokinetics following subcutaneous administration in subjects 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg. Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

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
6.2 Incompatibilities

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

6.3 Shelf life

4 years.

After reconstitution

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

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

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

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

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

Disposal

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Trading Services Limited
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 http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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 MANUFACTURERS 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 manufacturers responsible for batch release

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

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

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucala 100 mg solution for injection in pre-filled pen mepolizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each 1 ml pre-filled pen contains 100 mg mepolizumab.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also contains: sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, disodium edetate, water for injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection in pre-filled pen</td>
</tr>
<tr>
<td>Multipack: 3 (3 packs of 1) pre-filled pens.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Subcutaneous use.</td>
</tr>
<tr>
<td>For single use only.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
</table>
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

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
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
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**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucala 100 mg injection</td>
</tr>
<tr>
<td>mepolizumab</td>
</tr>
<tr>
<td>SC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
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 AUTHORIZATION HOLDER

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORIZATION 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 syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
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.

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

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

nucala syringe

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**
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 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 (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 AUTHORIZATION HOLDER**

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12. **MARKETING AUTHORIZATION 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)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucala 100 mg powder for solution for injection mepolizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each vial contains 100 mg mepolizumab (100 mg/ml after reconstitution)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients: Sucrose, sodium phosphate dibasic heptahydrate and polysorbate 80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder for solution for injection</td>
</tr>
<tr>
<td>Multipack: 3 (3 packs of 1) vials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use after reconstitution.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store below 25°C.</td>
</tr>
</tbody>
</table>
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 injection1 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 AUTHORIZATION HOLDER

GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

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

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

2. What you need to know before you use Nucala

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

➤ Check with your doctor if you think this applies to you.
Warnings and precautions
Talk to your doctor before using this medicine.

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

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

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

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

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

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

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

Children and adolescents
The pre-filled pen is not intended for use in children below 12 years of age.

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.

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

Other medicines for asthma

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

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

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

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

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.

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

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 asthma symptoms and attacks to come back.

If your asthma symptoms get worse while receiving injections of Nucala
⇒ Call your doctor.

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

4. **Possible side effects**

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

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

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

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

If you 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
• pharyngitis (sore throat)
• nasal congestion (stuffy nose)

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 pen.

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12 Riverwalk
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Dublin 24
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Manufacturer
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This leaflet was last revised in

Other sources of information

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

Before use

- Label
- Stopper
- Inspection window (medicine inside)
- Yellow needle guard (needle inside)
- Clear needle cap

After use

- Yellow indicator (becomes visible when the injection is complete)

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)

Do not perform the injection if you do not have all these.
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.

**Do not** inject where your skin is bruised, tender, red or hard.
**Do not** inject within 5 cm of your navel (belly button).

![Injection Site Diagram]

- Alternatively, another person can inject in your upper arm.
- Inject yourself in thighs or abdomen.
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.

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

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

2. What you need to know before you use Nucala

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

⇒ Check with your doctor if you think this applies to you.

Warnings and precautions
Talk to your doctor before using this medicine.
Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

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

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

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

⇒ Tell your doctor before you are given Nucala.

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

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

Children and adolescents
The pre-filled syringe is not intended for use in children below 12 years of age.
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.

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

Other medicines for asthma

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

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

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

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

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.
The recommended dose for adults and adolescents aged 12 years and older is 100 mg. You will have 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 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 asthma symptoms and attacks to come back.

If your asthma symptoms get worse while receiving injections of Nucala:

→ Call your doctor

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

4. Possible side effects

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

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

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

→ Seek medical attention immediately if you think you or your child may be having a reaction.

If you 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
• pharyngitis (sore throat)
• nasal congestion (stuffy nose)

**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.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu
7. Step by step instructions for using the 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 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

Before use
- White plunge
- White finger grip
- Stopper
- Inspection window (medicine
- Automatic needle guard
- Needle cap (needle inside)

After use
- After use, the automatic needle guard is activated and pulls up (retracts) the needle.

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)

Do not perform the injection if you do not have all these.
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.
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.

**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.

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**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.**
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
   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 and over.

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

Nucala can reduce your number of asthma attacks, if you or your child are already using medicines such as high dose inhalers, but your asthma is not well controlled by these medicines.

If you are taking medicines called oral corticosteroids, Nucala can also help reduce the daily dose you need to control your asthma.

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

2. What you need to know before you use Nucala

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

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

Warnings and precautions
Talk to your doctor before using this medicine.
Worsening asthma
Some people get asthma-related side effects, or their asthma may become worse, during treatment with Nucala.

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

Allergic and injection site reactions
Medicines of this type (monoclonal antibodies) can cause severe allergic reactions when injected into the body (see section 4, ‘Possible side effects’).
If you may have had a similar reaction to any injection or medicine,

⇒ Tell your doctor before you are given Nucala.

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

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

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

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

Other medicines for asthma

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

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

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

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

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).

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

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

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

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

If your asthma symptoms get worse while receiving injections of Nucala
➔ Call your doctor.

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

4. Possible side effects

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

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

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

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

If you (or your child) may have had a similar reaction to any injection or medicine:
➔ Tell your doctor before you are given Nucala.

Other side effects include:

Very common: 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
• pharyngitis (sore throat)
• nasal congestion (stuffy nose)

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.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
The following information is intended for healthcare professionals only:

Step-by-step instructions for use and handling, reconstitution, and administration
Nucala is provided as a lyophilised, white powder in a single-use vial for subcutaneous injection only. 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 1000 rpm for no longer than 5 minutes is acceptable.
3. Following reconstitution, Nucala should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be used.
4. The reconstituted solution, if not used immediately must be:
   - Protected from sunlight
   - Stored below 30°C, not frozen
   - Discarded if not used within 8 hours of reconstitution

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

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

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