Unit: Technical Assessment Unit

Public assessment report for biological products

(NUCALA)

Administrative information:

Trade name of the medicinal product:	**Nucala**
INN (or common name) of the active substance(s):	**Mepolizumab**
Manufacturer of the finished product	Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations), Harmire Road, Barnard Castle, County Durham, DL12 8DT, UNITED KINGDOM
Marketing Authorization holder	GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, IRELAND
Applied Indication(s):	**Severe eosinophilic asthma** Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults and adolescents. **Chronic rhinosinusitis with nasal polyps (CRSwNP)** Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. **Eosinophilic granulomatosis with polyangiitis. (EGPA)** Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA). **Hypereosinophilic syndrome (HES)** Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.
Pharmaceutical form(s) and strength(s):	**Solution of 100 mg for SC injection in prefilled pen**
Route of administration	**SC injection**

Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
BAL	Bronchoalveolar Lavage
CHO	Chinese hamster ovary
CLp	Total plasma clearance
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CV	Cardiovascular
CYP	Cytochrome P450
ECG	Electrocardiogram
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hIL-5	Human IL-5
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IL-5	Interleukin-5
IL-5Rα	Interleukin-5 Receptor alpha
ITT	Intention-To-Treat
IV	Intravenous
L-HES	Lymphocytic variant Hypereosinophilic Syndrome
mAb	Monoclonal antibody
mRNA	Messenger ribonucleic acid
NAb	Neutralizing Antibodies
nM & µM	Nanomolar & Micromolar
NP	Nasal Polyps
NPS	Nasal Polyp Score
OCS	Oral Corticosteroids
OLE	Open-Label Extension

(Nucala)

OR	Odds Ratio
PBS	Phosphate buffered saline
PD	Pharmacodynamic(s)
PFP	Pre-filled pen
PFS	Pre-filled syringe
rhIL-2	Recombinant human interluekin-2
rhIL-5	recombinant human IL-5
SB-240563	Mepolizumab (humanized anti-IL-5 mAb)
SB-240683	Humanized anti-IL-4 mAb and pharmacologically active in monkeys
SB-264091	Rat anti-human IL-5 mAb (homologous to mepolizumab)
SC	Subcutaneous
SEA	Severe eosinophilic asthma
t½	Terminal half-life
UK	United Kingdom
Vss	Volume of distribution at steady state
DS	drug substance

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1. Introduction

The finished product is a sterile liquid solution or infusion containing 100 mg/mL of Mepolizumab as active substance. Other ingredients are: sucrose, polysorbate 80, disodium dihydrate, sodium phosphate dibasic heptahydrate and citric acid monohydrate. Presented in a clear glass pre-filled syringe consisting of a type 1 glass siliconized barrel with a staked 29G thin wall stainless steel needle with a thermoplastic elastomer needle shield covered by rigid plastic shield sealed with fluororesin coated bromobutyl rubber plunger stopper. It is available in 100 mg dose (using a 1 mL fill volume)

2. Quality aspects:

2.1 Drug Substance (Active ingredient):

Mepolizumab drug substance is a clear to opalescent, colorless to pale yellow or pale brown solution.

Mepolizumab is a fully humanized monoclonal antibody (IgG1) targeted against human interleukin 5 (hIL-5). Mepolizumab binds and neutralizes soluble IL-5 which results in the inhibition of IL-5 signalling. This molecule consists of two light and two heavy chains.

- **Manufacturer:**

Human Genome Sciences, Inc. Belward Large Scale Manufacturing Facility, 9911 Belward Campus Drive, Rockville, MD 20850, USA - UNITED STATES OF AMERICA

- **Stability of drug substance**

  - Active Substance: 36 months, at the recommended storage condition of ≤ -35°C, protected from light

2.2 Drug product:

- **Description and Composition of the Drug Product:**

- The Drug product Mepolizumab Injection, 100 mg/mL is an aqueous solution containing the following: target quantities of excipients: 12% (w/v) sucrose, 0.02% (w/v) polysorbate 80, 0.05 mM, EDTA disodium dihydrate, 15.5 mM sodium phosphate dibasic heptahydrate and 4.5mM citric acid monohydrate at pH 6.3

Manufacturer:

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations), Harmire Road, Barnard Castle, County Durham, DL12 8DT, UNITED KINGDOM

Stability of the Drug product.

-Store in a refrigerator (2°C - 8°C) for 36 months.

-Do not freeze.

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

- If necessary, the pre-filled pen 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 must be administered within 8 hours once the pack is opened.

- The pack should be discarded if not administered within 8 hours

3. Non –clinical aspect:

- **Nucala (Mepolizumab or SB240563)** is a fully humanized CHO-derived monoclonal antibody (IgG1) targeted against human interleukin 5 (hIL-5, the key cytokine responsible for regulation of blood and tissue eosinophils). It is as a specific IL-5 antagonist indicated as an add-on therapy for long-term treatment of patients with conditions where eosinophilia plays an important part in the disease pathology such as refractory severe eosinophilic asthma (SEA), chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES). This product was first approved by the **FDA** in November 2015 for adults and children aged ≥12 with SEA. It was later approved for children aged 6 to 11 in 2019 and a 40 mg PFS for children in 2022. It was approved in December 2017 for adults with EGPA, in September 2020 as the first and only biologic treatment for HES and in July 2021 for adults with CRSwNP. This product was granted **EMA** approval on 02 December 2015.
- **Pharmacology:** Mepolizumab exhibited a PD response that was predicted for inhibiting IL-5 from binding to its receptor, resulting in a reduction in circulating and tissue eosinophils both in vitro and in vivo in monkeys. There was a delay in the manifestation of maximal effect (3 weeks after dosing) on basal eosinophil count. In addition, the marked peripheral blood eosinophilia induced by administration of rhIL-2 to the monkeys was blocked by >85% following a cycle of two ≥0.5mg/kg doses of mepolizumab. In studies to evaluate potential species cross-reactivity, mepolizumab had no effect on inhibiting cell proliferation or reducing the number of circulating eosinophils when tested in vitro using conditioned medium with IL-5 derived from various lower species or in some species following in vivo treatment. In monkeys, SB-240563 did not attenuate the acute bronchoconstrictor response to *Ascaris suum* antigen challenge. However, SB-240563 treatment resulted in a marked inhibition of pulmonary and peripheral blood eosinophilia in response to antigen challenge for at least 6 weeks following single IV dosing. Combination of mepolizumab and SB-240683 (the anti-IL-4 mAb) had no greater effect on eosinophil numbers or recruitment compared with mepolizumab alone. In a safety pharmacology study, there were no acute effects of mepolizumab on CV, respiratory and renal function or on body temperature after single or repeated IV doses of up to 100 mg/kg.
- **Pharmacokinetics:** The non-clinical PK profile of mepolizumab has been studied in rats, rabbits and monkeys. In monkeys, CLp and Vss of mepolizumab were low, and mepolizumab was highly bioavailable following SC

administration. Overall, the PK profile was similar for monkeys and humans, consistent with that expected of an IgG1 mAb, further validating the monkey as a suitable species for the nonclinical evaluation of mepolizumab. The t1/2 of mepolizumab in monkeys and humans is 2-3 weeks. Results from both PK comparability studies demonstrated that the test material used in the nonclinical development of mepolizumab was fully comparable with that used in clinical trials and also was comparable to the material proposed for marketing. Low concentrations of mepolizumab were detected in Bronchoalveolar Lavage (BAL) samples. In a reproduction and development study, high levels of mepolizumab were shown to cross the placenta and low levels were detected in milk. In an in vitro study using cultured hepatocytes, at concentrations of ≥1000 pg/ml, IL-5 and IL-6 reduced CYP3A4 mRNA levels by ≥69 and 77%, respectively. In general, PK analyses indicated that mepolizumab exposure was not limited by the development of immune antibody responses.

- **Toxicology:** In monkeys, single or monthly repeated IV doses of up to 304 or 100 mg/kg mepolizumab, respectively, resulted in decreased peripheral blood eosinophil by 80-100% and were reversible following the cessation of treatment with no evidence of toxicological effects. The antagonism of IL-5 had no effect on reproductive function, pregnancy or development of the offspring in a fertility and early embryonic/embryofoetal development assessment of SB-264091 (a rat anti-human IL-5 mAb, ≤50 mg/kg) in mice and a pre- and postnatal development study with mepolizumab (≤100 mg/kg) in monkeys. However, mepolizumab crosses the placental barrier and the teratogenic potential of mepolizumab was not studied in the monkey pre- and post-natal study. The effect of mepolizumab on human pregnancy is unknown; hence, mepolizumab should only be administered if the potential benefit to the mother outweighs the potential risks to the fetus. There were also no effects on the general health or immunologic development of offspring evaluated for 9 months pp. In local tolerance evaluations, IV or SC administration of mepolizumab was well tolerated with no local reactions. Using immunohistochemistry, mepolizumab binding was demonstrated to be restricted to human lymphoid tissues in vitro, consistent with the distribution of the target epitope (IL-5), suggesting little likelihood for non-pharmacologic effects. The weight of evidence for mepolizumab suggests that the risk for potential immunotoxicity is low. Nonclinical data imply that mepolizumab treatment has the potential to antagonize clearance of some helminth infections (e.g., *M. corti*) but does not increase the chances of initial infection or prevent establishment of sterile immunity. Mepolizumab was weakly immunogenic in the battery of toxicology studies conducted in monkeys using IV and SC routes. In these studies, only 3% of the animals generated ADAs, which resulted in enhanced systemic clearance of mepolizumab but no adverse reactions. The inhalation delivery study demonstrated the general feasibility of pulmonary delivery of mepolizumab and also indicated the likelihood of enhanced immunogenicity, which reflects a route-dependent antibody response or delivery of the test material via the nebulizer in a modified (aggregated) form, thereby altering its presentation to the immune system.
- **Overall conclusion:**

This nonclinical overview presents an integrated and critical assessment of the pharmacologic, PK and toxicologic evaluation of mepolizumab and supports the safe use of mepolizumab for the treatment of patients for the approved indications as recommended in the prescribing information.

4. Clinical aspect:

➢ Clinical Overview

The clinical development program for Nucala (mepolizumab) spans multiple eosinophil-driven diseases, including SEA, HES, EGPA and CRSwNP.

Its mechanism of action targeting interleukin-5 (IL-5) is well established and directly linked to suppression of eosinophilic inflammation.

The clinical evidence package is comprehensive and aligned with International Council for Harmonization Good Clinical Practice standards.

Overview of Key Clinical Studies

➢ Clinical Efficacy:

Efficacy in severe eosinophilic asthma is supported by **three pivotal placebo-controlled trials (MEA112997, MEA115588, MEA115575),** demonstrating clinically meaningful reductions in exacerbations and oral corticosteroid (OCS) use, supported by pharmacology and long-term extension studies.

In HES, evidence is primarily derived from a single pivotal Phase III study (200622), supported by open-label extension data and earlier studies, demonstrating reductions in disease flares.

In EGPA, one pivotal Phase III study (MEA115921) demonstrated increased remission rates and duration, with paediatric extrapolation justified based on disease rarity.

In CRSwNP, the pivotal Phase III study (205687) demonstrated improvements in nasal polyp size and nasal obstruction, supported by a Phase II study.

For the liquid formulation, comparability with the lyophilized formulation was demonstrated through PK studies and supported by real-world use and human factor studies confirming safe and effective self-administration.

➢ Clinical Safety

Overall, mepolizumab demonstrates a favorable and consistent safety profile across all indications, supported by extensive exposure data and long-term follow-up.

Severe Eosinophilic Asthma

The safety database is robust (n=2022 exposed; 1018 at 100 mg SC), with long-term exposure (86% ≥12 months). Adverse drug reactions were identified using a structured and regulatory-compliant methodology.

No increased risk of malignancy, serious infections, or cardiovascular events

Lower incidence of serious adverse events (SAEs) vs placebo (mepolizumab 100 mg SC (6%) and 75 mg IV (10%) vs placebo (15%)

Deaths were rare and unrelated to treatment

No clinically relevant laboratory, ECG, or systemic toxicity signals

Hyper eosinophilic Syndrome (HES)

High overall AE rates (~90%) consistent with disease burden

Increased incidence of upper respiratory tract infections and some AEs with relative risk >2

Higher rate of serious infections (9% vs 1%)

Lymphoma cases likely confounded by disease subtype (e.g., lymphocytic variant HES) and high-dose exposure

Slight imbalance in cardiovascular events, likely related to baseline comorbidities

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

High AE incidence (~95%) in both arms
Most events mild to moderate
Hypersensitivity reactions were rare and manageable
Serious infections lower than placebo
One death (cardiac) not related to treatment
Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
Comparable AE incidence (~80%) between groups
Increased injection-site reactions and hypersensitivity
Reduced serious infections and cardiovascular events
No treatment-related SAEs or deaths
One death (cardiac) not related to treatment (in placebo group) **Liquid Formulation**
Low AE incidence in real-world and healthy volunteer studies
No treatment-related SAEs or deaths
Comparable safety to lyophilized formulation

- **Clinical Immunogenicity**

Mepolizumab demonstrates low immunogenic potential across all indications:
ADA incidence: ~2- 6%
Neutralizing antibodies: rare or absent
No impact on pharmacokinetics, pharmacodynamics, efficacy, or safety
This profile is consistent across asthma, HES, EGPA, CRSwNP, and the liquid formulation.

- **Overall Conclusion**

The clinical data package for mepolizumab is comprehensive and robust:
Pharmacokinetics and pharmacodynamics are well characterized
Efficacy is demonstrated across all indications, with strongest evidence in asthma, EGPA, and CRSwNP
Safety profile is favourable and consistent with mechanism of action
Immunogenicity is low and clinically insignificant
Remaining uncertainties include:
Limited data in elderly (>82 years) and pregnant populations
Limited paediatric data in some indications (addressed via extrapolation and post-marketing commitments)
Some methodological limitations in exposure–response analyses
Despite these, the totality of evidence supports the proposed indications and dosing regimen

- **Benefit–Risk Analysis**

The overall benefit- risk balance of mepolizumab (Nucala) is considered positive across all approved indications.
Benefits
Significant reduction in exacerbations in severe eosinophilic asthma
Reduction in oral corticosteroid dependence
Decreased disease flares in HES
Increased remission rates in EGPA
Improvement in nasal polyp burden and symptoms in CRSwNP

Sustained and consistent reduction in blood eosinophil levels

Risks and Uncertainties

Increased risk of serious infections in HES

Hypersensitivity and injection-site reactions

Limited data in elderly, paediatric (some indications), and pregnant populations

Lack of dedicated QT/DDI studies (scientifically justified)

Unclear exposure–response relationship for some endpoints

All identified risks are manageable through routine pharmacovigilance and risk minimisation measures, and are adequately reflected in product information.

**Taking into account the demonstrated efficacy, acceptable safety profile, low immunogenicity, and well-understood mechanism of action, the overall benefit–risk balance of mepolizumab remains favourable.

5. General Conclusion and Recommendations if any:

Recommendation:

Approval is supported across all proposed indications and formulations, with routine risk management and continued post-marketing surveillance.

EPAR:https://www.ema.europa.eu/en/documents/variation-report/nucala-h-c-003860-p46-020-epar-assessment-report_en.pdf