Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Mepolizumab

Proprietary Product Name: Nucala

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
ACQ	Asthma Control Questionnaire
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curved from time zero (dosing) to time infinity
C-ACT	Childhood Asthma Control Test
CI	Confidence interval
CL/F	Apparent clearance
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
EMA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (US)
FEV_1	Forced expiratory volume-in one second
FEV_1/FVC	Ratio of forced expiratory volume in one second to forced vital capacity (Tiffeneau-Pinelli ratio)
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HES	Hypereosinophilic syndrome
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IgG1	Immunoglobulin G1
IL-5	Interleukin 5
IL-5Rα	Interleukin 5 receptor α
LABA	Long-acting beta (β)-agonists

Abbreviation	Meaning
NO	Nitric oxide
OCS	Oral corticosteroids
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pop PK	Population pharmacokinetic(s)
PSUR	Periodic safety update report
RMSE	Root mean square error
SABA	Short-acting beta (β)-agonist
SAE	Serious adverse event
SC	Subcutaneous
$t_{1/2}$	Biological half-life
UK	United Kingdom
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Rejected
Date of decision:	25 July 2019
Date of entry onto ARTG:	Not applicable
ARTG number:	Not applicable
, *Black Triangle Scheme*	Not applicable
Active ingredient:	Mepolizumab
Product name:	Nucala
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne VIC 8003
Dose form:	Powder for injection
Strength:	100 mg
Container:	Vial
Pack size:	One
Approved therapeutic use:	Not applicable
Route of administration:	Subcutaneous
Dosage:	*Proposed* *Children aged 6 to 11 years old* The recommended dose is 40 mg of mepolizumab administered by subcutaneous (SC) injection once every 4 weeks. For instructions on attaining a 40 mg dose from the vial, see Method of Administration below. Each 100 mg vial of mepolizumab should be used for a single patient, and the remainder of the vial should be discarded. The safety and efficacy of Nucala have not been established in children less than 6 years of age.

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register Nucala (mepolizumab) 100 mg powder for injection for the following extension of indications:

> *Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 6 years and over.*

Asthma is a heterogeneous disease characterised by narrowing and swelling of the airways, leading to chest tightness, wheezing, shortness of breath and cough. It affects 1 to 18% of the population globally.[1]

Asthma severity is assessed from the level of treatment required to control symptoms and exacerbations. Severe asthma is defined as asthma that requires treatment with medium/high dose inhaled corticosteroids (ICS) and long-acting β-agonists (LABA), to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this treatment. In general, the definition of severe asthma is reserved for patients with refractory asthma and those in whom response to treatment of comorbidities is incomplete.

Different asthma 'phenotypes' or 'endotypes' have been described based on clusters of demographic, clinical and/or pathophysiological characteristics. Inflammation in severe asthma has been categorised into eosinophilic, neutrophilic and/or paucigranulocytic.

Severe refractory eosinophilic asthma is a small subgroup of the total population diagnosed with asthma. In adults, eosinophilia appears to be associated with higher risk of exacerbations, and less response to ICS or oral corticosteroids (OCS). Studies in adults found high blood eosinophilia count (³ 400/mm^3) was associated with increased future asthma exacerbations and short-acting β-agonist (SABA) use after adjustment of potential confounders. Sputum eosinophilia appears more stable in adults over longer yearly periods but less so in children.

Severe asthma is less frequent in paediatric age groups than in adults but the severity is greater as evidenced by the higher frequency of emergency department (ED) visits and hospitalisations. Asthma that is difficult to control may require the addition of OCS, with known adverse effects particularly in children. Children with severe asthma are often highly atopic with increased peripheral blood eosinophilia, aeroallergen sensitivity, and elevated serum immunoglobulin E (IgE) concentrations, with sustained increases in exhaled nitric oxide (NO).

According to the Global Initiative for Asthma (GINA);[1] additional treatment options (in addition to medium or high-dose ICS plus LABA) for children over 6 years whose asthma is difficult to control, include the following:

- tiotropium; trade name 'Spiriva': in Australia '*indicated as add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate to severe asthma*'; and
- omalizumab; trade name 'Xolair': in Australia indications include '*In children aged 6 to < 12 years, Xolair is indicated as add-on therapy to improve asthma control in patients with severe allergic asthma who have documented exacerbations despite daily high dose inhaled corticosteroids, and who have immunoglobulin E levels corresponding to the recommended dose range*'.

[1] Global Initiative for Asthma (GINA). Report: Global Strategy for Asthma Management and Prevention, 2018. Available from the GINA website.

The inflammatory response involving eosinophils is potentially a cause of smooth muscle hypertrophy and chronic mucosal damage associated with airway remodelling and asthma exacerbations.

Mepolizumab is a humanised monoclonal antibody (immunoglobulin G1 (IgG1), kappa) directed against human interleukin-5 (IL-5). IL-5 is a major haematopoietic cytokine responsible for growth and differentiation of eosinophils. Mepolizumab blocks the binding of IL-5 to the alpha chain of the IL-5 receptor (IL-5Rα) complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Regulatory status

Nucala (mepolizumab) 100 mg powder for injection received initial registration on the Australian Register of Therapeutic Goods (ARTG; AUST R 232028) on 2 February 2016 for the following indication:

> *Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over (see Clinical Trials).*

On 24 January 2019, the following extension of indications was approved:

> *Relapsed or refractory EGPA*
>
> *Nucala is indicated as an add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over (see section 5.1 Pharmacodynamic Properties - Clinical Trials).*

As such, the full indications at this time were:

> *Severe refractory eosinophilic asthma*
>
> *Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over (see Section 5.1 Pharmacodynamic Properties - Clinical Trials).*
>
> *Relapsed or refractory EGPA*
>
> *Nucala is indicated as an add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over (see section 5.1 Pharmacodynamic Properties - Clinical Trials).*

At the time the TGA considered this application, a similar application for the treatment of children with severe refractory eosinophilic asthma aged 6 years and older had been approved in the European Union (EU; approved on 27 August 2018) and was under consideration in Switzerland, the United States (US), Chile, Canada, Japan, Russia, Saudi Arabia, Brazil and Taiwan (see Table 1).

Table 1: International regulatory status as of 21 May 2019

Region	Submission date	Status	Indications
European Union (centralised procedure) Rapporteur: United Kingdom (UK) Co-Rapporteur: Ireland	21 November 2017	Approved 27 August 2018	*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).*
Switzerland	20 December 2017	Under consideration	Under consideration
United States (US)	16 November 2018	Under consideration	Under consideration
Chile	12 March 2019	Under consideration	Under consideration
Canada	27 March 2019	Under consideration	Under consideration
Japan	28 March 2019	Under consideration	Under consideration
Russia	29 March 2019	Under consideration	Under consideration
Saudi Arabia	28 March 2019	Under consideration	Under consideration
Brazil	22 April 2019	Under consideration	Under consideration
Taiwan	8 May 2019	Under consideration	Under consideration

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-00537-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	18 June 2018
First round evaluation completed	30 November 2018
Sponsor provides responses on questions raised in first round evaluation	31 January 2019
Second round evaluation completed	4 March 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 May 2019
Sponsor's pre-Advisory Committee	21 May 2019

Description	Date
response	
Advisory Committee meeting	7 June 2019
Registration decision (Outcome)	25 July 2019
Completion of administrative activities and registration on ARTG	Not applicable
Number of working days from submission dossier acceptance to registration decision*	226

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The sponsor has proposed a partial extrapolation model to bridge the indication in severe eosinophilic asthma between adults and children. This was agreed with the European Union (EU) paediatric committee of the European Medicines Agency (EMA).

The data submitted in support of the extension of indication included:

- Study 200363 part A; a pharmacokinetic (PK)/pharmacodynamic (PD) study;
- Study 200363 part B; a safety study with secondary efficacy endpoints;
- Study 200862; a supportive study;
- a population pharmacokinetic (pop PK) analysis; and
- a dose modelling simulation report.

Pharmacology

Study 200363

This was an open label, un-blinded study to characterise the PK and PD of mepolizumab administered subcutaneously (SC) in children age 6 to 11 years with severe eosinophilic asthma.

Data from adults and pop PK modelling were used to inform the dose selection.

Part A

- Conducted at 13 centres;
- Comprised pre-screening, 12 week treatment period, and an 8 week follow up;
- inclusion criteria included:
  - Age 6 to 11 years;
  - Severe asthma;
  - Eosinophilic airway inflammations (characterised by blood eosinophils ³ 300 cells/µL within 12 months or ³ 150 cells/µL at Visit 1);
  - Treated with medium or high dose ICS + other controller;
  - Persistent airway inflammation (forced expiratory volume inone second (FEV_1) < 110% or forced expiratory volume to forced vital capacity ratio (FEV_1/FVC) < 0.8);
  - 2 exacerbations in the past 12 months.

Treatment

Mepolizumab 100 mg if ³ 40 kg or 40 mg if < 40 kg.

Results

Of the 44 patients enrolled, 7 did not meet the inclusion/exclusion criteria and one did not meet the continuation criteria due to an exacerbation. This left 36 that were enrolled to mepolizumab SC treatment.

Pharmacokinetic results and population pharmacokinetics

The historical adult 'target value' for exposure, based on the Phase III exacerbation Study MEA115588, expressed as area under the concentration time curve (AUC) was 343 µg.day/mL. The estimated area under the concentration-time curve from time zero (dosing) to time infinity ($AUC_{0\text{-}inf}$) (95% confidence interval (CI)) for the ³ 40 kg group receiving 100 mg SC was 675.20 µg.day/mL (602.2 to 748.2). This is approximately 1.97 times this historical adult target exposure.

For the < 40 kg group receiving 40 mg SC, the corresponding $AUC_{0\text{-}inf}$ (µg.day/mL) (95% CI) estimate was 454.39 (422.1 to 486.7). This is approximately 1.32 times the historical target adult value for AUC.

The biological half-life ($t_{1/2}$) was approximately 23 days, comparable to previous adult data (16 to 22 days).

Apparent clearance (CL/F) in children (normalised to 70 kg) was lower than that observed in adults. Bodyweight-adjusted apparent clearance (that is, CL/F at 70 kg) point estimate 0.20 L/day (90% CI: 0.17 to 0.22) fell outside the 80% to 125% historical adult point estimate and range values of 0.29 L/day (80% to 125% interval: 0.23 to 0.36).

Exploratory popPK analysis estimated a higher SC absolute bioavailability of 105% (95% CI: 55 to 155%), rather than a lower clearance, as the most likely explanation for the difference in apparent clearance in the 6 to 11 years old population. This compares to an estimated bioavailability in adults of 74 to 80%.

The popPK analysis used two compartment approach. Factors that affect exposure include body weight and bioavailability.

Study 2014N223530

This study described the extrapolation of adult PK pop PK modelling to the paediatric setting, identified optimal doses and weight bands for severe asthma, and made recommendations for dosing based on body weight.

Study 2018N368753

This was an additional PK analysis following the results of Study 200363 and provided an alternative age based dosing regime for children aged from 6 to 11 years. This analysis was initiated following feedback from the US Food and Drug Administration (FDA) on the initial weight based dosing regimen proposal of 40 mg for children < 40 kg and 100 mg for children ³ 40 kg that resulted in exposures up to 2 times that seen in adults. The discrepancy was thought to be due to lower apparent clearance (attributed to increased bioavailability in paediatric patients). This analysis simulated exposure following a flat dose of 40 mg in all patients age 6 to 11 years over a weight range of 15 to 70 kg.

A dosing regimen of mepolizumab 40 mg SC every 4 weeks for children aged between 6 to 11 years without any dose adjustment for body weight was simulated over the weight range 15 to 70 kg. The root mean square error (RMSE) for this dose was 25% of the adult target exposure for 15 to 50 kg weight group. Over the weight band 50 to 70 kg, the optimal dose ratio to the adult 100 mg dose was 0.87 and further adjustment was not warranted (it is unclear what implications this has on children > 50 kg).

Pharmacodynamic response

The baseline blood eosinophil counts in the entire population was 370 cells per microlitre. There were similar reductions in blood eosinophils in the 40 and 100 mg mepolizumab groups.

Efficacy

Study 200363

Part A

Baseline features: weight ranged from 20.2 to 60.6 kg; FEV_1 was 90%. 19% were on medium dose ICS, 81% on high dose ICS. 34 (94%) were taking LABA, 28 (78%) were taking leukotriene receptor antagonists, 24 were on systemic corticosteroids. Other treatments included tiotropium (1 patient), antibiotics (4 patients), mucolytics (6 patients), cromoglycate sodium (5 patients).

Efficacy was a secondary or exploratory endpoint.

At Week 12, a ³ 0.5 point reduction from Baseline in the Asthma Control Questionnaire 7 and 5 (ACQ-7; ACQ-5) questionnaires was observed in 48% and 55% of subjects overall respectively.

Childhood Asthma Control Test (C-ACT) scores showed only minor improvements.

Changes from Baseline in pre-bronchodilator FEV_1 were variable.

Exacerbations on treatment were as follows in Table 3.

Table 3: Asthma exacerbations on-treatment, Study 200363

	Mepo SC 40 mg (weight <40 kg) (N=26)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC (N=36)
Exacerbation			
Any, n (%)	8 (31)	2 (20)	10 (28)
Number of events	10	3	13
1, n (%)	6 (23)	1 (10)	7 (19)
2, n (%)	2 (8)	1 (10)	3 (8)
Exacerbations requiring hospitalisation or hospitalisation or emergency room visit			
Number of subjects, n (%)	4 (15)	0	4 (11)
Number of events	5	0	5
Exacerbations requiring hospitalisation			
Number of subjects, n (%)	3 (12)	0	3 (8)
Number of events	3	0	3

Source Data: Table 2.19 and Table 2.20

Note: The baseline is defined as the latest value recorded prior to the first dose of mepolizumab.

Part B

30 subjects from Part A continued into Part B and continued treatment for a further 52 weeks, and 20 have continued into a long term access programme. In the 12 months prior to screening, these patients had on average 3.5 exacerbations per year and in around 40% hospitalisation was required.

- Safety: 90% had any adverse events (AE) and 23% had any serious adverse events (SAE).
- PD: There was an 86.5% reduction in blood eosinophils.
- Clinical efficacy: at the exit visit, a ³ 0.5 point reduction from Baseline was seen in 55% for the ACQ-7 and 59% for ACQ-5. There was a numerical improvement in asthma control. FEV_1 pre-bronchodilator increased by an average of 278 mL. There were 14 subjects that had 31 exacerbations, and 5 subjects required hospitalisation. 80% had a more than 50% decrease in exacerbations, 7% had an increase in exacerbations compared to Baseline prior to study entry.

Safety

In children and adolescents aged 6 to 17 years with severe asthma, 26 children were exposed to 40 mg and 42 children and adolescents were exposed to 100 mg. The mean duration of exposure in those exposed to 40 mg was 2.7 months, the mean duration of exposure for those administered 100 mg was 9.9 months, 24 patients had been exposed for > 12 months.

In clinical studies of adults and adolescents, mepolizumab is well tolerated. In the integrated Phase III placebo-controlled severe asthma studies, AEs were reported in similar numbers of the placebo and active treatment groups. The most frequently reported AEs were headache and nasopharyngitis.

Study 200363 in children aged 6 to 11 years was not placebo controlled, thus it is not possible to determine if adverse events were treatment related. Headache and injection site reactions were the most common on treatment events in Study 200363 Part A.

The safety data submitted by the sponsor included data from clinical studies in other disorders such as hypereosinophilic syndrome (HES). This patient population have a

different risk profile due to a different underlying disorder and different dose given. It is noteworthy that 4 paediatric patients in the HES compassionate use program have died.[2] The causes of death included disease progression, malignancy, sepsis and respiratory failure.

In Study 200363 Part A in children aged 6 to 11 years with severe asthma, 6 subjects reported 18 on treatment serious adverse events. Two subjects had serious adverse events that were considered to be potentially related to study treatment by the investigator. One subject had severe back and chest pain, dizziness, headache, nausea and pain resulting in admission to hospital and treatment with morphine. This event occurred 8 days after the first dose and lasted 2 weeks; the events resolved. No further doses were given. Another subject had an exacerbation of asthma 38 days after the first dose of mepolizumab (11 days after the second dose) that led to discontinuation of mepolizumab treatment and withdrawal from the study. The asthma exacerbation resolved in 10 days.

In the most recent periodic safety update report (PSUR) including data until March 2018, 3303 subjects had been exposed to mepolizumab in completed GSK sponsored interventional clinical studies. There were 11 new post-marketing reports of anaphylaxis received during the period covered by the PSUR (24 September 2017 to 23 March 2018).

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[3]

Risk-benefit analysis

Delegate's considerations

Discussion

The main issue with this submission is the role of extrapolation to support the efficacy and safety of mepolizumab in children with eosinophil asthma. Table 4 outlines the Delegate's views about the extrapolation concept. However, the Delegate notes that the EMA accepted this.

The Delegate is uncertain if eosinophilic asthma is a recognised entity in children. The Delegate is also unsure if serum eosinophils are a sensitive biomarker for eosinophilic asthma in children, and if the patients in the clinical trial were indicative of patients in the community with eosinophilic asthma.

The clinical data in the paediatric population is very limited. It includes only a small number of patients in a non-controlled study followed for 12 months. This being said, the efficacy data does support the efficacy of mepolizumab in children with severe asthma and high eosinophil count for endpoints FEV_1, exacerbations and quality of life. There were no new safety concerns in children.

The dose proposed in children is justified by PK data.

[2] Sponsor comment/clarification: Patients in the HES compassionate use program have severe disease with organ- or life-threatening disease.
[3] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

Table 4: Delegate's opinion of extrapolation model

Sponsor's reasoning	Delegate's comment
Benefits shown for use of mepolizumab in adults with severe eosinophilic asthma justify extrapolation of the use of mepolizumab in children with severe eosinophilic asthma with who meet the criteria for eosinophil count	This is acceptable only if it can be demonstrated that condition is the same in adults in children eosinophil count in children predicts tissue eosinophils and is diagnostic of eosinophilic asthma. There is very limited information about the role of biomarkers in children. Thus, the value of eosinophils in diagnosing eosinophilic asthma in children is unknown.
Mepolizumab PK in adults is predictive of mepolizumab PK in children	This is not entirely true; the SC absorption is greater in children. However, the sponsor has proposed a dose in children based on age and weight that will result in a similar exposure to that in adults.
Mepolizumab blood eosinophil count reduction in adults is seen in children	This is true. However, there is no evidence that the reduction in blood eosinophils is the direct PD effect, nor that a reduction in blood eosinophils correlates with efficacy.
Mepolizumab efficacy in adults can be compared to adolescents	Adolescents have more similar physiology than adults, and asthma in adolescents shared some features of adults with asthma. Adolescents were a small part of the clinical development program in patients aged > 12 years. Subgroup analysis was not performed due to low number.
Evidence in adolescents is sufficient to extend the approach to the 6 to 11 year old group	This depends upon other criteria being met.
Safety in 6 to 11 year olds is similar to that seen in adults	This is true, however only a relatively small number of subjects have been studied. There is limited information about the use of 40 mg dose over 12 months.

Summary of issues

- The extrapolation model was built upon the assumptions around similarity of eosinophilic asthma in paediatric and adults:
  - 'eosinophilic asthma' is rare in children;
  - children have a different 'normal range' for blood eosinophils, and eosinophilia has different causes in children than adults;
  - there is no evidence of a correlation between blood and tissue or airway eosinophils in 'paediatric eosinophilic asthma'; and
  - severe asthma in adults and children is different; children get more exacerbations from allergies and viral illnesses and FEV_1 is relatively higher.
- There was a small single arm clinical trial; efficacy was a tertiary endpoint.
- Dosing in the clinical trial was stratified by weight (< or > 40 kg). However, due to high exposures with such dosing, age based dosing is proposed. The new dosing model has not been tested.

Proposed action

The Delegate was not in a position to say, at the time, that the application for Nucala should be approved for registration for use in children aged 6 to 11 years (inclusive) with eosinophilic asthma.

Request for ACM advice

1. Is eosinophilic asthma a recognised clinical entity in children? How is it diagnosed? Is the population of children in the clinical trial typical of those with eosinophilic asthma?
2. Please comment on the frequency of atopy in the clinical trial. Can we be sure the high eosinophils are due to eosinophilic asthma and not atopy?

Advisory Committee considerations[4]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Nucala, a powder for injection containing 100 mg of mepolizumab.

The proposed indication considered by the ACM was:

> *Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 6 years and over (see Clinical Trials).*

The ACM agreed that Nucala had an overall negative benefit-risk profile for the proposed indication as the evidence submitted did not satisfactorily support the extrapolation strategy.

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. Is eosinophilic asthma a recognised clinical entity in children? How is it diagnosed? Is the population of children in the clinical trial typical of those with eosinophilic asthma?

The ACM advised that eosinophilic asthma is a rare condition in children and difficult to diagnose. The clinical trial inclusion criteria relied on elevated eosinophil blood levels as an indicator for eosinophil airway inflammation; however, the ACM advised that eosinophilic asthma should not be diagnosed solely on blood elevated eosinophils.

The ACM advised that there was insufficient evidence to use eosinophil count as a biomarker for eosinophilic asthma. Some children diagnosed with eosinophilic asthma may have normal blood eosinophils counts and therefore a large proportion of patients would be excluded if diagnosis was based solely on blood eosinophil count. Further, the ACM advised that many children with elevated eosinophil counts have other explanations

[4] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

and that therefore elevated eosinophil counts would frequently be a false positive marker for eosinophilic asthma.

2. Please comment on the frequency of atopy in the clinical trial. Can we be sure the high eosinophils are due to eosinophilic asthma and not atopy?

The ACM advised that the frequency of atopy in the clinical trial was expectedly high and that the high eosinophil count may be due to atopy and not necessarily due to eosinophilic asthma.

General advice

With respect to efficacy, the ACM noted that the primary aim of the PK/PD study (Study 200363) was to characterise the PK of mepolizumab to support extrapolation for paediatric use. It was noted that the PK characteristics of mepolizumab in children differed from those in adults due to differences in bioavailability. The efficacy data in this clinical study was limited due to the small number of patients and the lack of a control group.

The ACM considered there to be insufficient evidence to support the extrapolation strategy for paediatric use, given:

- the age-related differences in pharmacokinetic data;
- the criteria for diagnosing eosinophilic asthma in children; and
- the lack of comparative efficacy data demonstrating significant benefit in adolescents and children.

The ACM was of the view that, given the paucity of information regarding use of mepolizumab in children, further studies, such as the current ongoing long-term clinical trial, should be conducted to provide sufficient evidence to support the proposed indication.

Outcome

Based on a review of quality, safety and efficacy, the TGA rejected the registration of Nucala (mepolizumab) 100 mg powder for injection for the proposed therapeutic indication:

> *Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in patients aged 6 years and over.*

Reasons for the decision

The Delegate of the Secretary's major consideration is whether 'the quality, safety and efficacy of the good for the purposes for which it is to be used have been satisfactorily established'.

The sponsor used a partial extrapolation model and a small open label, non-randomised clinical study in children to support the use of mepolizumab in children aged 6 to 12 years with eosinophilic asthma. The main reason for the Delegate's decision to reject this application is that they do not agree with the extrapolation model proposed by the sponsor.

The EMA reflection paper on extrapolation in paediatrics;[5] recommends generating data about the disease, drug pharmacology and clinical response to treatment in the paediatric

[5] European Medicines Agency (EMA), Reflection paper on the use of extrapolation in the development of medicines for paediatrics, 7 October 2018, EMA/189724/2018

and adult populations from either published studies or other sources. This information is required before an assessment of the similarity of disease, similarity of drug pharmacology, and similarity of effect of the drug can be established.

The Delegate disagrees with the assumption that paediatric eosinophilic asthma is diagnosed using the same criteria as in adults. Published data has demonstrated that serum eosinophils are not an appropriate marker of airway eosinophilia in children, and that eosinophilia in children may be due to other disease that are not asthma.

There is no information to support the similarity between paediatric eosinophilic asthma and adult eosinophilic asthma in terms of physiology, and natural history. Publications included by the sponsor demonstrated that children and adolescents with severe asthma have different clinical features to adults. In a report by Fitzpatrick 2012;[6] children and adolescents with severe asthma were more likely to be atopic and have higher eosinophils and IgE, and less likely to have airflow limitation. Similar findings were supported clinical study by Phipatanakul 2017,[7] and also baseline data from the sponsor's clinical development program in document 2017N323587.Therefore, the assumption that children with severe asthma and elevated eosinophils have the same 'disease' as adults with severe asthma and elevated eosinophils is not justified.

The sponsor has stated that extrapolation of efficacy in adults to adolescents justifies the extrapolation of adolescents to children. The TGA has not 'extrapolated' data from adults to adolescents. In the studies supporting the use of mepolizumab in patients aged > 12 years with severe eosinophilic asthma, patients aged > 12 years were enrolled in the study however adolescents (aged 12 to 18 years) represented only a small proportion (4%) of the total population. It is a not appropriate to analyse efficacy in such a small subgroup. Efficacy in that subgroup has not been directly demonstrated, but was inferred, as they were part of the larger study.

Although the endpoints for asthma used in clinical trials are similar for children and adults, the relative importance and expected changes differ. For example, adults with severe asthma have lower FEV_1 at baseline than children, thus are more likely to have a response to treatment. On the other hand, children tend to get more exacerbations due to viral illness and allergy, adults may develop exacerbations due to co-morbid conditional such as chronic obstructive pulmonary disease (COPD) or occupational exposure or heart failure. Subjective symptom scales are likely to be recorded differently in a child and adult.

The paediatric study submitted was acceptable to assess the PK and PD of mepolizumab, however was not appropriate to assess efficacy for a number of reasons. The Delegate's main concern is that it was a single arm open label study, and it is therefore not known if changes in disease parameters are due to the medication or a study effect. The Delegate is also concerned about the use of adult criteria to define eosinophilic asthma in children, and that the patient population enrolled may not be representative of children with eosinophilic asthma. In children, there is a poor correlation between serum eosinophils and airway eosinophilia.[6,8] This would have led to misclassification bias, both due to false positives (for example, children with eosinophilia due to allergy who may not have airway eosinophilia), and false negatives (for example, in children on oral or inhaled steroids).

The sponsor has proposed the extrapolation of safety from adults to children in view of the similar safety outcomes demonstrated in the clinical trials. However, the appropriate duration of treatment in children has not been established. The total lifetime exposure to a

[6] Fitzpatrick, A.M. et al. (2012), Severe asthma in childhood: recent advances in phenotyping and pathogenesis, *Curr Opin Allergy Clin Immunol*, 2012, 12: 193-201.
[7] Phipatanakul, W. et al. (2017), Effects on age and disease severity on systemic corticosteroid responses in asthma, *Am J Respir Crit Care Med*, 2017; 195: 1439-1448.
[8] Ullman, N et al (2013). Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. Allergy, 2013; 68: 402-406.

drug for a chronic disease started in childhood is much greater than one commenced in adulthood. There are other safety issues that must be assessed in children such as the impact of a medicine on the developing immune system and fertility.

The ACM and experts contacted were also of the opinion that there was insufficient data to support the use of mepolizumab in children with severe eosinophilic asthma at this stage. More studies to better characterise eosinophilic asthma in children are required. And clinical studies need be adequately powered, controlled, and of longer duration.

It is noted that there is a randomised, placebo controlled clinical trial in urban children with the severe asthma (Study MUPPITS-2), due for completion in September 2019 with an estimated number 320 children participating. The sponsor is National Institute of Allergy and Infectious Diseases, the sponsor is listed as a collaborator.[9]

Conclusion

The Delegate is of the opinion that there is insufficient evidence at this time to support the efficacy of mepolizumab in children aged 6 to 11 years (inclusive) with severe eosinophilic asthma.

Future applications for this indication should include more information about how paediatric eosinophilic asthma is defined clinically, including relevant biomarkers, and a comparative controlled clinical study.

[9] A Trial of Mepolizumab Adjunctive Therapy for the Prevention of Asthma Exacerbations in Urban Children (MUPPITS-2), ClinicaTrials.gov identifier: NCT03292588.

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