Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Indacaterol (as acetate) / glycopyrronium (as bromide) / mometasone furoate

Proprietary Product Name: Enerzair Breezhaler

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

April 2021

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
β_2	Beta 2
AAN	Australian Approved Name
ACM	Advisory Committee on Medicines
ACQ-7	Asthma Control Questionnaire 7
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AusPAR	Australian Public Assessment Report
BID	Twice a day (Latin: *bis in die*)
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	Confidence interval
CMI	Consumer Medicines Information
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EMEA	European Medicines Evaluation Agency (European Union)
EU	European Union
FDC	Fixed dose combination
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma

Abbreviation	Meaning
GVP	Good Pharmacovigilance Practices
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroid(s)
IgE	Immunoglobulin E
LABA	Long-acting beta 2 (β_2)agonist
LAMA	Long-acting muscarinic receptor antagonist
LS	Least squares
M_3	Muscarinic acetylcholine 3
MSD	Merck Sharp and Dohme
OCS	Oral corticosteroid(s)
OD	Once daily
OIP	Orally inhaled product
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic safety update report
QVM149	Drug product development code for Enerzair Breezhaler
RCT	Randomised controlled trial
RMP	Risk management plan
RR	Risk ratio
SABA	Short-acting beta 2 (β_2)agonist
SD	Standard deviation
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order

I. Introduction to product submission

Submission details

Type of submission:	New combination of active ingredients
Product name:	Enerzair Breezhaler
Active ingredients:	Indacaterol (as acetate) / glycopyrronium (as bromide) (glycopyrrolate) / mometasone furoate
Decision:	Approved
Date of decision:	9 October 2020
Date of entry onto ARTG:	20 October 2020
ARTG numbers:	319002, 319001
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd PO Box 101 North Ryde NSW 1670
Dose form:	Inhalation powder in hard capsule
Strengths:	Fixed dose combination of 150 µg indacaterol, 50 µg glycopyrronium and 80 µg mometasone furoate (delivered dose of 114 µg indacaterol (as acetate), 46 µg glycopyrronium (as bromide) and 68 µg mometasone furoate) Fixed dose combination of 150 µg indacaterol, 50 µg glycopyrronium and 160 µg mometasone furoate (delivered dose of 114 µg indacaterol (as acetate), 46 µg glycopyrronium (as bromide) and 136 µg mometasone furoate)
Container:	Blister pack
Pack sizes:	Ten Enerzair capsules, with one Breezhaler inhaler 30 Enerzair capsules, with one Breezhaler inhaler

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Approved therapeutic use:	*Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.*
Route of administration:	Inhalation
Dosage:	**Adult patients** Inhalation of the content of one capsule of Enerzair Breezhaler, delivering 114 µg indacaterol (as acetate)/46 µg glycopyrronium (as bromide)/68 µg mometasone furoate or 114 µg indacaterol (as acetate)/46 µg glycopyrronium (as bromide)/136 µg mometasone furoate once daily (OD) is the recommended dose. The maximum recommended dose (delivered dose) is Enerzair Breezhaler 114/46/136 µg OD. Patients should be prescribed Enerzair Breezhaler containing the appropriate dosage of mometasone furoate for the severity of their disease. Treatment should be based on individual patient's benefit risk assessment and regularly reassessed by a healthcare professional. For further information regarding dosage, refer to the Product Information (PI).
Pregnancy category:	B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The Therapeutic Goods Administration (TGA) does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Enerzair Breezhaler (indacaterol (as acetate)/glycopyrronium (as bromide) (glycopyrrolate)/mometasone furoate) 150 µg/50 µg/80 µg (delivered dose 114 µg/46 µg/68 µg); 150 µg/50 µg/160 µg (delivered dose 114 µg/46 µg/136 µg) inhalation powder in hard capsule for the following proposed indication:

> *Enerzair Breezhaler is indicated as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid.*

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterised by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness and underlying inflammation. Clinical characteristics and treatment response of asthmatics are heterogeneous.[2,3] In older patients, there may be substantial overlap with features of chronic obstructive pulmonary disease (COPD) and patients with asthma COPD overlap are at higher risk of exacerbations and complications. In Australia, one in nine Australians have asthma. Deaths attributed to asthma have remained stable over past five years at 1.5 deaths per 100,000 population. Asthma is associated with poorer quality of life, with disease severity and the level of control both having an impact.

The main objective in asthma treatment is to maintain asthma control. Asthma control is defined as '*the extent to which the various manifestations of asthma have been reduced or removed by treatment*'. This concept encompasses two components, the patient's recent clinical status/current disease impact (symptoms, night awakenings, use of reliever medication and lung function) and future risk (exacerbations, decline in lung function or treatment related side effects). The long term goals of asthma management are to achieve good symptom control and to minimise future risk of exacerbations, fixed airflow limitation and side effects of treatment. According to the Global Initiative for Asthma (GINA) guidelines, asthma is controlled when a patient has daytime symptoms only twice or less per week, has no limitation of daily activities, has no nocturnal symptoms and no exacerbations, has normal or near normal lung function and uses reliever medication twice or less per week.[4]

GINA proposes a classification of asthma severity by the type and intensity of controller medication required for the control of the disease (a Step 1 to 5 classification) for investigational purposes. GINA also proposes a classification in three categories (mild, moderate and severe asthma) assessed retrospectively once the patient is on regular controller treatment for several months. Asthma is considered mild when the patient's disease requires a short-acting beta 2 (β_2) agonist (SABA) alone or is controlled with low dose maintenance inhaled corticosteroids (ICS) and a SABA as needed. The stepwise approach to therapy, in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible, is used to achieve and maintain asthma control.

The GINA workshop report classifies drug treatments as controllers or relievers. Controllers are taken daily and long term and include both anti-inflammatory drugs (ICS, leukotriene modifiers, anti-immunoglobulin E (IgE) treatment, and oral corticosteroids (OCS)) and long-acting beta 2 (β_2) agonists (LABA). Relievers are medications used on an

[2] Jones, T. L. et al. Diagnosis and Treatment of Severe Asthma: a Phenotype-based Approach, Clin Med (Lond), 2018; 18 (Suppl 2): s36-s40.
[3] Barnes, P. J. Triple Inhalers for Obstructive Airways Disease: Will They be Useful?, Expert Rev Respir Med, 2011; 5(3): 297-300.
[4] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020.

as needed basis to reverse bronchoconstriction and relieve symptoms (for example, SABAs and one LABA). A new category has recently been included, that is add-on therapies for patients with severe asthma, which include additional therapeutic options that may be considered when patients have persistent symptoms and/or exacerbations despite optimised treatment with high dose controller medications and treatment of modifiable risk factors. In addition, allergen immunotherapy is available for allergic asthma although its specific role is not established yet.

A LABA plus ICS (LABA/ICS combination) is a well-established therapy class with a known safety profile. GINA guidelines define LABA/ICS as the cornerstone asthma therapy for GINA Step 3 patients and above. Patients with asthma not adequately controlled on a medium or high dose LABA/ICS combination (preferred treatment option in patients ≥ GINA step 4) have airway obstruction reflected by objective spirometry assessment of forced expiratory volume in one second (FEV_1), are symptomatic and are at risk to develop exacerbations. Other optional therapies for patients at GINA Step 4 include the addition of tiotropium (a long-acting muscarinic receptor-antagonist (LAMA)) to medium or high dose LABA/ICS treatment regimen or the addition of a leukotriene receptor antagonist or low dose sustained release theophylline to medium or high ICS (which is less efficacious than the addition of LABA).[5] At GINA Step 5, therapeutic alternatives are even more limited and include addition of tiotropium, referral to a specialist and addition of biologic therapy (for example, anti IgE, or anti interleukin-5 therapy) that is specifically recommended only in a subpopulation (for example, for severe allergic asthma or asthma with an eosinophilic phenotype). The addition of low dose OCS is another option but is often associated with substantial systemic side effects.[5]

The addition of tiotropium to high dose LABA/ICS treatment improved lung function and delayed the time to first severe exacerbation, with a significant reduction of 21% in the risk of severe exacerbation.[6,7,8] Although the three classes of drugs (LABA, LAMA and ICS) are approved treatments for asthma, there is currently no fixed dose combination (FDC) product of the three approved for the treatment of asthma. ICS is the cornerstone treatment in asthma. The mechanisms of action of LABA and LAMA classes are complementary due to the differential density of beta 2 (β_2) adrenoceptors and muscarinic acetylcholine (M_3) receptors in smaller versus central airways, respectively.[9,10,11]

Non-adherence to medication is a major cause of poor control of asthma and may be related to several factors including difficulty using inhalers properly, complicated regimens (for example, multiple times per day, multiple different inhalers) and misunderstanding of the role of controller medications.[5] Adherence is higher with the combination ICS/LABAs than when the components are administered separately.[12] Poor treatment adherence is one of the identified risk factors for future exacerbations,

[5] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018.
[6] Kerstjens, H. A. M. et al. Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy, N Engl J Med, 2012; 367(13):1198-1207.
[7] Halpin, D. M. Tiotropium in Asthma: What is the Evidence and How Does It Fit in, World Allergy Organ J, 2016; 9(1):29.
[8] Kerstjens, H. A. M. et al. Tiotropium Improves Lung Function, Exacerbation Rate, and Asthma Control, Independent of Baseline Characteristics Including Age, Degree of Airway Obstruction, and Allergic Status. Respir Med, 2016; 358:198-206.
[9] Carstairs, J. R. et al. Autoradiographic Visualisation of Betaadrenoceptor Subtypes in Human Lung, Am Rev Resp Dis, 1985; 132(3):541-547.
[10] Mak, J. C. W. and Barnes, P. J. Autoradiographic Visualization of Muscarinic Receptor Subtypes in Human and Guinea Pig Lung, Am Rev Resp Dis, 1990; 141(6):1559-1568.
[11] Ikeda, T. et al. Regional Quantification of Muscarinic Acetylcholine Receptors and β-adrenoceptors in Human airways, Br J Pharmacol, 2012; 166(6):1804-1814.
[12] Murphy, K. R. and Bender, B. G. Treatment of Moderate to Severe Asthma: Patient Perspectives on Combination Inhaler Therapy and Implications for Adherence, J Asthma Allergy, 2009; 2:63-72.

independent of the symptom control.[5] Hence, there is an unmet need for new asthma therapies that offer sustained bronchodilation combined with anti-inflammatory properties, with effective asthma control and that decrease the risk of future exacerbations.

Enerzair Breezhaler (QVM149;[13]) is a novel approach of combining an orally inhaled LABA/LAMA/ICS in a once daily (OD) FDC of indacaterol acetate (a LABA); glycopyrronium bromide (a LAMA); and mometasone furoate, an ICS. It is intended as a maintenance treatment for asthma in adult patients. QVM149 is formulated as lactose blended inhalation powder hard capsules delivered by the Concept 1 device.[14] These medicines have mechanisms of actions that complement each other. Following inhalation, indacaterol is a LABA that acts locally by widening the airways in the lungs. It has a rapid onset of action and a long duration of action. Glycopyrronium is an inhaled LAMA (anticholinergic) which dilates the airways by blocking the action of the neurotransmitter acetylcholine on smooth muscle cells. Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and anti-inflammatory properties. The individual components of QVM149 are widely authorised as monotherapies or as a combination product for the treatment of either COPD (indacaterol and glycopyrronium) or asthma (mometasone furoate) with established efficacy and a well characterised safety profile. There was no clinically relevant pharmacokinetic interaction between the individual components when administered together as a FDC.

Regulatory status

This product is considered a new combination of active ingredients for Australian regulatory purposes.

At the time the Therapeutic Goods Administration (TGA) considered this application, a similar applications were approved in the European Union (EU) (submitted in May 2019), Japan (submitted on 30 July 2019), and Canada (submitted on 22 July 2019) and an application was under consideration in Singapore (submitted on 11 December 2019) and Switzerland (submitted on 6 June 2019).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	May 2019	Approved on 3 July 2019	*Enerzair Breezhaler (150/50/160 µg) is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.*

[13] QVM149 is the drug development code for Enerzair Breezhaler used by the sponsor.
[14] Concept1 device is the device development code used by the sponsor, approved in Australia as the Breezhaler device.

Region	Submission date	Status	Approved indications
Japan	30 July 2019	Approved on 29 June 2020	*Enerzair (150/50/80 µg and 150/50/160 µg) approved indication: Bronchial asthma (in case requiring combination use of inhaled corticosteroid, inhaled long acting beta 2 adrenergic agonist and inhaled long-acting anticholinergic agent).*
Singapore	11 December 2019	Under consideration	Under consideration
Canada	22 July 2019	Approved on 2 July 2020	*Enerzair Breezhaler (150/50/160 µg) is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a medium or high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous 12 months.*
Switzerland	6 June 2019	Approved on 24 September 2020	*Enerzair Breezhaler is indicated as a maintenance treatment in asthma and to improve lung function in adults for whom a maintenance combination of a long-acting beta2 agonist and inhaled corticosteroid does not offer sufficient control.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-02514-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	5 March 2020
Sponsor provides responses on questions raised in first round evaluation	14 April 2020
Second round evaluation completed	25 May 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 July 2020
Sponsor's pre-Advisory Committee response	23 July 2020
Advisory Committee meeting	7 August 2020
Registration decision (Outcome)	9 October 2020
Completion of administrative activities and registration on the Australian Register of Therapeutic Goods (ARTG)	20 October 2020
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.

TGA guidance at pre-submission meetings is nonbinding and without prejudice.

Relevant guidelines for evaluation of this submission are:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 22 October 2015. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Asthma (CHMP/EWP/2922/01 Rev.1).
- European Medicines Evaluation Agency (EMEA), CHMP, 19 February 2009. Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1).
- CHMP, 22 January 2009. Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence between Two Inhaled Products for Use in the Treatment of

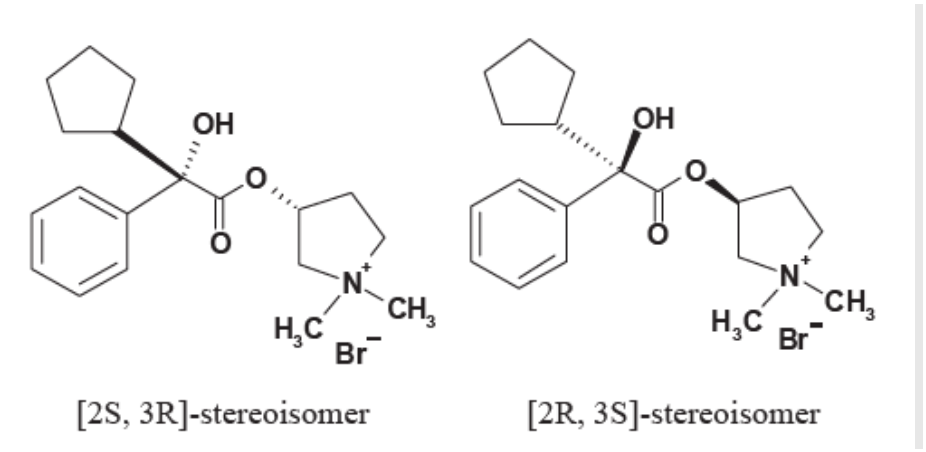
Asthma and COPD in Adults and for Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 Rev. 1).

- EMEA, November 1994. Dose Response Information to Support Drug Registration (CPMP/ICH/378/95).

Quality

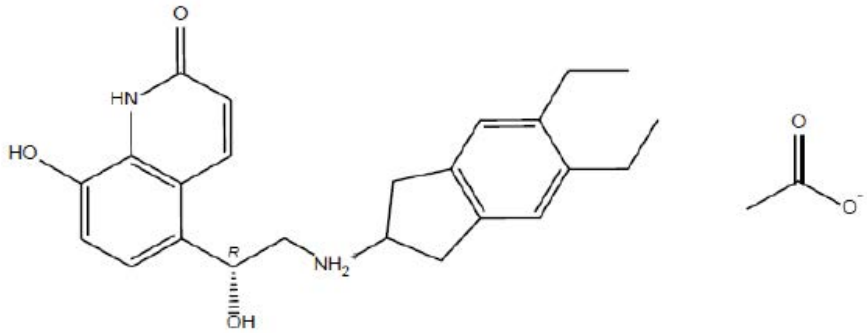
Glycopyrronium bromide is stated to be of the same quality as that currently used in the sponsor's Seebri Breezhaler.[15] Prior to harmonisation of the Australian Approved Name (AAN), glycopyrronium bromide was known as glycopyrrolate. Glycopyrronium bromide contains two asymmetric carbon atoms and is an optically inactive racemic mixture of two stereoisomers (2S, 3R and 2R, 3S). The chemical structure of glycopyrronium bromide is shown in Figure 1.

Figure 1: Chemical structure of glycopyrronium bromide



Indacaterol acetate is manufactured from the same starting materials and using the same route of synthesis as the indacaterol maleate used in the registered monotherapy inhalation product Onbrez Breezhaler.[16] Quality aspects of indacaterol acetate have been assessed in connexion with the related submission for Atectura Breezhaler.[17] The chemical structure of indacaterol acetate is shown in Figure 2.

Figure 2: Chemical structure of indacaterol acetate

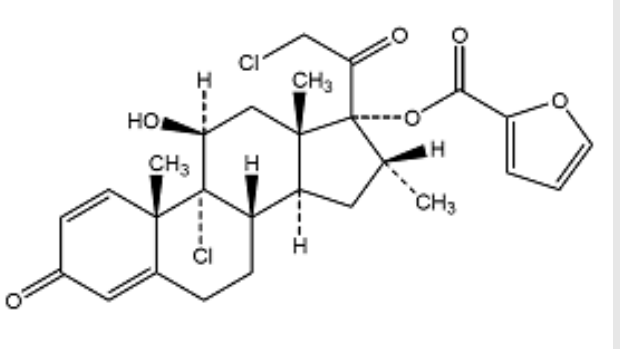


Mometasone furoate is currently marketed as a monotherapy product, Asmanex Twisthaler, by Merck, Sharp and Dohme (MSD). The drug substance to be used for this

[15] Seebri Breezhaler was first registered on the ARTG on 12 November 2012 (ARTG number: 191517).
[16] Onbrez Breezhaler was first registered on the ARTG on 3 August 2010 (ARTG number: 160172 and 160177).
[17] Atectura Breezhaler was first registered on the ARTG on 21 July 2020 (ARTG number: 319074, 319075 and 319076).

product is stated to be the same quality as that currently used in the EU market and Asmanex in Australia (AUST R 73725 and 73726. The chemical structure of mometasone furoate is shown in Figure 3.

Figure 3: Chemical structure of mometasone Furoate



The powder for inhalation is contained within single use capsules, packaged in blisters with a dosing device (inhaler) that is integral to product delivery. The device (Breezhaler), is the same as that used for other inhalation products currently registered by the sponsor (for example, Onbrez Breezhaler indacaterol (as maleate), Ultibro Breezhaler;[18] indacaterol (as maleate)/glycopyrronium (as bromide) and, Seebri Breezhaler glycopyrronium (as bromide)).

Packs containing 10, 30, 90 and 150 capsules are proposed in the PI document. Each inhaler device has an in-use life of 90 inhalations so the 10 and 30/90 capsule packs will include one inhaler device while the 150 capsule packs will include 15 inhalers.

Monotherapy products (Onbrez Breezhaler indacaterol (as maleate), Seebri Breezhaler glycopyrronium (as bromide) and Asmanex mometasone furoate) are available in packs of; 10, 30 and 60 capsules (inhalations) and 10, 30 and 90 capsules, and 14, 30 and 60 capsules respectively. The company should be asked to confirm the proposed pack sizes as the PI states pack sizes of 10, 30, 90 and 150 capsules while labels are only provided for 10, 30 and 150 capsule packs. Additionally, the company should be asked to justify the proposed pack sizes, particularly the 10 and 150 pack sizes.

The quality evaluator has recommended approval of this product if the labelling will be updated as delivered dose.

Therapeutic Goods Order (TGO) 91;[19] (section 11(2)(h)) requires that dry powder inhalers express the quantity of the active ingredient as:

i. The quantity delivered per actuation,

ii. or where the secretary, when registering the medicine, has accepted that the dose of products containing those active ingredients was clinically established as the metered dose, then, the quantity metered per actuation.

The company has proposed to label the products as the metered doses, that is, the amount of active ingredient contained within the capsules, rather than the delivered dose. The company has justified this approach as follows:

'[The sponsor] has applied for the metered dose to be included on the labels for Enerzair for consistency with the other Breezhaler registered products (Onbrez, Ultibro and Seebri).

[18] Ultibro Breezhaler was first registered on the ARTG on 21 March 2014 (ARTG number: 206449).
[19] **TGO 91**: Therapeutic Goods Order 91; Standards required for labels of prescription and related medicines; made under Section 10 of the Therapeutic Goods Act (1989).This Order sets out what kinds of information are required to be included on the label of prescription and other related medicines. For further information, visit the TGA website: https://www.tga.gov.au/therapeutic-goods-orders.

These other inhalation products were registered prior to TGO 91 implementation and since they contain the same dosage device, we believe it is justified to continue to use the metered dose on Enerzair to reduce prescriber confusion.'

The Delegate agrees with the quality evaluator's conclusion and has made this requirement as a condition for registration.

All outstanding quality, manufacturing and labelling issues have been revolved. Approval is recommended for registration of the proposed product from a quality perspective.

Nonclinical

There are no nonclinical objections to the registration of Enerzair Breezhaler. The nonclinical evaluator has recommended approval of this product.

Treatment involves one inhalation OD. The metered doses of the active ingredients 150 µg indacaterol, 50 µg glycopyrronium and up to 160 µg mometasone furoate do not exceed that approved for inhalational administration of the single agents. Delivered doses of indacaterol and mometasone furoate also do not exceed that already approved, while the delivered dose of glycopyrronium is marginally increased (46 µg with this product in comparison with 44 µg with Seebri Breezhaler) but exposure in patients is reported to be comparable.

Indacaterol is present in this product as the acetate salt, in contrast to all existing indacaterol containing products, which use the maleate salt.

Nonclinical module contained no studies with the triple combination, but was adequate in scope, in accordance with International Council for Harmonisation (ICH);[20] M3 (R2).[21] It was composed mostly of data submitted in a concurrent application to register indacaterol acetate and mometasone furoate in dual combination (Atectura Breezhaler). Some studies submitted and evaluated for the original registration of Seebri Breezhaler were re-provided. The single new nonclinical study concerned the mutagenic potential of impurities of glycopyrronium bromide.

The combination of these three pharmacological classes is not novel. Previously evaluated *in vitro* studies with dual combinations have shown additive inhibition of bronchoconstriction with glycopyrronium and indacaterol and enhanced effects on the expression of a number of asthma related genes with indacaterol and mometasone furoate.

No pharmacokinetic interaction between the three agents is predicted from *in vitro* data on enzyme/transporter inhibition and from knowledge of the routes of metabolism. Pharmacokinetics were reported to not be affected with co-administration in humans.

Previously evaluated inhalational repeat dose toxicity studies with indacaterol/glycopyrronium and indacaterol/mometasone furoate in in rats and dogs do not suggest novel or clinically relevant additive toxicity with the triple combination.

The acetate and maleate salts of indacaterol exhibited no difference in kinetics or toxicity in rats and/or dogs in studies evaluated for Atectura Breezhaler.

[20] The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.
[21] ICH M3 (R2) Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals.

Pregnancy Category B3,[22] as the sponsor proposes, is considered to be appropriate, based on reference to existing data for the individual components.

The nonclinical evaluator has required the sponsor to make amendment in the draft PI as directed.

Clinical

The clinical dossier consisted of

- one Phase III study (Study CQVM149-B2302);
- three supportive studies; and
- six pharmacokinetic (PK)/ pharmacodynamic (PD) studies.

Pharmacology

The delivered dose for Enerzair Breezhaler 150 µg indacaterol/ 50 µg glycopyrronium/ 80 µg mometasone furoate is equivalent to 114 µg indacaterol, 46 µg glycopyrronium, and 68 µg mometasone furoate.

The delivered dose for Enerzair Breezhaler 150 µg indacaterol/ 50 µg glycopyrronium/ 160 µg mometasone furoate is equivalent to 114 µg indacaterol, 46 µg glycopyrronium, and 136 µg mometasone furoate.

As both active components are currently approved as monotherapies, the clinical pharmacology studies submitted were in support of the proposed FDC.

Findings of the PK studies indicate that both the indacaterol acetate and maleate salts are bioequivalent. Indacaterol is presented as the acetate salt in triple inhaler and the maleate salt in the TGA approved monotherapy product-Onbrez inhaler.

The dose selection of mometasone furoate in QVM149 was based on the dose of mometasone furoate in previously approved Asmanex Twisthaler. QVM149 was delivered via a new device (Concept 1) and mometasone furoate was in a new formulation.

A three step bridging approach demonstrated that the dose of mometasone furoate delivered by Concept 1 device was proportionate to the corresponding dose of mometasone furoate delivered by Twisthaler.[23]

Based on the PK data from the pivotal study, in asthmatics, steady state systemic exposure of individual components of QVM149 was comparable when administered individually or as a FDC.

The sponsor concluded that there was no PK drug to drug interaction between individual components of QVM149. This assumption was based on the finding that the systemic exposure was comparable when individual components of QVM149 were administered individually and as a FDC.

The sponsor's rationale for dose finding for pivotal studies in asthmatics appears reasonable. The proposed doses of indacaterol acetate, glycopyrronium bromide and mometasone furoate are comparable to products with these active ingredients and

[22] **Australian Pregnancy Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[23] Asmanex Twisthaler was first registered on ARTG on 18 June 2001 (ARTG code: 73725 and 73726).

currently approved by TGA for the use in patients with COPD as a monotherapy or FDC. This approach is in line with previously approved FDCs for COPD and asthma.

Efficacy

The dossier included one pivotal study. No other studies that assessed efficacy as a primary objective were included in this submission.

A Phase III study to assess efficacy endpoints as secondary objective was included in the dossier. This study was conducted in patients with moderate to severe asthma.

Study CQVM149-B2302 (pivotal study)

Study CQVM149-B2302 was a Phase III 52-week duration randomised controlled trial (RCT).

The primary objective was to demonstrate superiority of:

- either QVM149 150/50/80 µg OD to QMF149;[24] 150 µg indacaterol/160 µg mometasone furoate OD at 26 weeks; or
- QVM149 150/50/160 µg OD to QMF149 150 µg indacaterol/320 µg mometasone furoate OD, in terms of change from Baseline in trough FEV_1 at 26 weeks.

Similarly, the secondary objective was to demonstrate superiority of either of the triple FDCs to corresponding dual therapies;[25] in terms of Asthma Control Questionnaire 7 (ACQ-7).[26]

The primary and secondary endpoints were measured at 26 weeks of treatment period.

Study design

All eligible patients were using LABA/ICS therapy for at least three months and been on stable medium or high dose LABA/ICS for at least one month prior to Visit 1. During the run-in period, all patients received an open label medium dose of salmeterol xinafoate/fluticasone propionate 50/250 µg twice a day (BID). Patients meeting the eligibility criteria at the end of run-in period were randomised to one of the five treatment groups as follows:

QVM149 150/50/80 µg OD

QVM149 150/50/160 µg OD

QMF149 150/160 µg OD

QMF149 150/320 µg OD

salmeterol xinafoate/fluticasone propionate 50/500 µg BID

All these QVM149 and QMF149 treatments were delivered via the Concept 1 device (Breezhaler); salmeterol xinafoate/fluticasone propionate 50/500 µg BID was delivered via the Accuhaler device.

[24] QMF149 is the device development code for Twisthaler used by the sponsor.
25 The term corresponding dose of dual therapies in this file note is referring to the doses of QMF149 that were compared to the QVM149. The doses of MF in the QVM and QMF inhalers that were compared in this study are not equivalent.
[26] The **Asthma Control Questionnaire 7** (**ACQ-7**) is a multidimensional 7 item questionnaire assessing symptoms (5 items, patient responses), rescue bronchodilator use (1 item, patient response), and the one second forced expiatory volume as a percentage of predicted (FEV_1%; 1 item) completed by clinic staff. The ACQ-7 measures the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

Key inclusion criteria

The key inclusion criteria were:

- adults with confirmed diagnosis of asthma and required medium or high dose of LABA/ICS combinations for asthma for ≥ three months and still symptomatic with ACQ-7 score ≥ 1.5.
- at least one asthma exacerbation which required medical care or hospitalisation in the 12 months prior to Visit 1, and required OCS treatment.

Baseline data

Mean age was around 52 years, with a mean duration of asthma for around 18 years. The mean ACQ-7 score was 2.51 (standard deviation (SD), 0.567). Approximately 80% of the patients had a history of one asthma exacerbation and 19.7% of the patients had a history of two or more asthma exacerbations during the 12 months prior to the screening. The mean pre-bronchodilator percent predicted FEV_1 at the start of run-in (Visit 101) was 54.8%.

Results

Primary endpoint: trough forced expiratory volume in one second at Week 26:

At Week 26 of treatment period, both QVM149; indacaterol/ glycopyrronium bromide/ mometasone furoate 150/50/160 µg and 150/50/80 µg OD were superior to corresponding doses of ICS/LABA (QMF149; indacaterol/ mometasone furoate 150/320 µg and 150/160 µg OD) in terms of change from Baseline in trough FEV_1 (see Table 3).

Patients treated with the triple inhaler therapy with the high dose ICS (160 µg mometasone furoate) achieved a change in FEV_1 from Baseline that was 65 mL greater than those treated with a corresponding dose of ICS/LABA. Those who were treated with the triple inhaler with the medium dose of ICS (80 µg mometasone furoate) achieved a change in FEV_1 from Baseline that was 76 mL greater than those treated with a corresponding dose of ICS/LABA.

Table 3: Study CQVM149-B2302 Primary endpoint

						----- Treatment difference ----		
Visit	Treatment	n	Absolute value LS Mean (SE)	Change from baseline LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
Day 184	QVM 150/50/160	541	2.050 (0.0128)	0.320 (0.0128)	QVM 150/50/160 - QMF 150/320	0.065 (0.0176)	(0.031, 0.099)	<.001
					QVM 150/50/160 - S/F 50/500	0.119 (0.0177)	(0.085, 0.154)	<.001
	QVM 150/50/80	538	2.029 (0.0129)	0.299 (0.0129)	QVM 150/50/80 - QMF 150/160	0.076 (0.0176)	(0.041, 0.111)	<.001
					QVM 150/50/80 - S/F 50/500	0.099 (0.0177)	(0.064, 0.133)	<.001

The improvement in FEV_1 appears to be sustained at 52 weeks, a least squares (LS) mean (treatment difference) of 0.086 and 0.062 for high and medium dose QVM149, compared to their corresponding doses of QMF149 (see Table 4).

Table 4: Study CQVM149-B2302 Readout of forced expiratory volume in one second at Week 52

Day 365	QVM 150/50/160	532	2.050 (0.0129)	0.321 (0.0129)	QVM 150/50/160 - QMF 150/320	0.086 (0.0176)	(0.051, 0.120)	<.001
					QVM 150/50/160 - S/F 50/500	0.145 (0.0178)	(0.111, 0.180)	<.001
	QVM 150/50/80	512	1.992 (0.0130)	0.263 (0.0130)	QVM 150/50/80 - QMF 150/160	0.062 (0.0178)	(0.027, 0.096)	<.001
					QVM 150/50/80 - S/F 50/500	0.087 (0.0179)	(0.052, 0.122)	<.001

Both high and medium doses of QVM149 achieved similar magnitude of improvement in trough FEV_1, compared to both QMF149 and salmeterol 50 µg/fluticasone 500 µg inhaler.

Key secondary endpoint, Asthma Control Questionnaire-7:

There was no significant treatment difference in terms of asthma control between both doses of QVM149 and corresponding doses of QMF149 at Week 26 and Week 52. The secondary endpoint was not met.

The LS mean change from Baseline in ACQ-7 was -0.977 and -0.963 with high and medium doses of QVM149, -0.997 and -0.902 with high and medium doses of QMF149 at Week 26, respectively.

The ACQ-7 responder rates were about 70% for all treatment groups after 26 weeks.

Other secondary endpoints:

No significant difference was reported in Asthma Quality of Life Questionnaire (AQLQ) scores between QVM149 doses and between corresponding doses of QMF149.

The magnitude of improvement for lung function parameters such as forced vital capacity (FVC) and forced expiratory flow (FEF) 25 to 75% were comparable for both doses of QVM149.

In the first clinical study report (CSR; the primary analysis CSR), the incidence rate (annualised) of exacerbations was the lowest in high dose QVM149 group, among all treatment groups. A 20% greater reduction in all exacerbations (risk ratio (RR) = 0.80, 95% confidence interval (CI): 0.65, 0.98) and 17 % greater reduction in severe exacerbations (RR = 0.83, 95% CI: 0.64, 1.07) were reported for the high dose QVM149, compared to high dose QMF149. High dose QVM149 reduced all asthma exacerbations by 41% versus salmeterol/fluticasone 50/500 µg BID (RR = 0.59, 95% CI: 0.48, 0.72).

A 10% greater reduction in all exacerbations (RR = 0.90, 95% CI: 0.74, 1.10) and 6% greater reduction in severe exacerbations (RR = 0.94, 95% CI: 0.74, 1.19) were reported for medium dose QVM149 group, compared to medium dose QMF149 group. Medium dose QVM149 demonstrated a reduction in the rate of all exacerbations by 30% (RR = 0.70, 95% CI: 0.58, 0.84) compared to salmeterol/fluticasone 50/500 µg BID.

The magnitude of reduction in exacerbations reached statistical significance for the comparison between high dose QVM149 and high dose QMF149, and not for comparison between medium dose QVM149 and medium dose QMF149.

The magnitude of reduction in exacerbations was consistent in the second CSR (full analysis set CSR) (see Table 5).

Table 5: Study CQVM149-B2302 Rate of asthma exacerbations at Week 52 (full analysis set)

Exacerbation category Treatment	n	Annualized rate (95% CI)	Comparison	Rate ratio	(95% CI)	p-value
All (mild, moderate, severe) asthma exacerbation						
QVM 150/50/160 (N=615)	615	0.74 (0.64, 0.85)	QVM 150/50/160 / QMF 150/320	0.79	(0.66, 0.96)	0.016
			QVM 150/50/160 / S/F 50/500	0.60	(0.50, 0.72)	<.001
QVM 150/50/80 (N=616)	615	0.86 (0.75, 0.98)	QVM 150/50/80 / QMF 150/160	0.87	(0.72, 1.06)	0.161
			QVM 150/50/80 / S/F 50/500	0.70	(0.58, 0.84)	<.001
QMF 150/320 (N=611)	611	0.93 (0.82, 1.06)				
QMF 150/160 (N=607)	607	0.98 (0.86, 1.11)				
S/F 50/500 (N=612)	612	1.23 (1.08, 1.39)				

n = number of patients included in the analysis

No differences in use of rescue medication was reported between treatment groups.

The Delegate noted that both high and medium doses of QVM149 were compared to the same (high) dose of salmeterol/fluticasone.

Safety

Safety data was mostly based on observations from the pivotal study. Pooled data of QVM149 doses were also compared to corresponding QMF149 and salmeterol/fluticasone dose to assess safety.

Adverse events

The majority of adverse events (AE) were mild to moderate in severity and their occurrence was similar between the treatment groups. Asthma exacerbations were the commonest AEs that was reported and its rate of incidence was lower in QVM group, compared to QMF group. Oral candidiasis occurrence rates were lower in the QVM149 pooled group than in the QMF149 pooled group (0.7 versus 1.2) and were also lower in the QVM149 high dose group than the salmeterol/fluticasone 50/500 µg BID group (0.2 versus 2.1).

Treatment emergent adverse events

In the pivotal study, asthma was the commonest reported treatment emergent adverse event (TEAE), followed by nasopharyngitis. The incidence rate for both these events were highest in QVM149 high dose group, compared to all other treatment groups. Incidence rate of dysphonia in the high dose QVM group was 4.2, compared to 1.8 in the high dose QMF group and 2.1 in salmeterol/fluticasone group.

The incidence rate of pneumonia was comparable across treatment groups.

The incidence rate of cardiac disorders was 4.4 in high dose QVM group, compared to 3.3 in high dose QMF group and 3.4 in salmeterol/fluticasone group.

At 52 weeks, the high dose QVM group experienced higher cumulative incidence for tachycardia (1.34 versus 0.5) and dysphonia (3.99 versus 2.15), compared to medium dose QVM group.

Seven deaths were reported during study period. Two deaths were reported in the QVM149 high dose group: one patient died due to cardiac tamponade and aortic dissection; another patient died due to sudden cardiac death (reported as pulmonary

embolism by the investigator). None of the deaths were determined as related to the study treatments.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.0 (dated 16 April 2019; data lock point (DLP) 27 October 2018) and Australia specific annex (ASA); version 1.0 (dated 17 June 2019) in support of this application.

In a TGA request for information, the sponsor submitted EU-RMP version 1.2 (dated 18 February 2020; DLP 14 June 2019) and no updated ASA.

In response to the second round RMP evaluation report, as part of the Delegate's overview, the sponsor has provided EU-RMP version 1.3 (dated 21 April 2020; DLP 14 June 2019) and ASA version 1.1 (dated 17 July 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.[27]

Table 6: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Serious cardiovascular events	ü*†‡§	–	ü‖	–
Missing information	Asthma patients < 18 years and > 75 years^	ü	–	ü	–
	Use in pregnancy and lactation^	ü	–	ü	–

*Follow-up checklist for ischemic heart disease/myocardial infarction

†Follow-up checklist for cardiac conduction abnormalities

‡Follow-up checklist for acute and congestive heart failure

§Follow-up checklists for stroke

‖Instruction for use (package insert)

^Australian specific safety concerns

[27] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The RMP evaluator has concluded that:

- The proposed summary of safety concerns was considered generally acceptable. The sponsor was asked to include asthma patients < 18 years and > 75 years as missing information and to align the summary of safety concerns with that for Ultibro Breezhaler. The sponsor has provided adequate justification for not including 'asthma patients < 18 years and > 75 years' as missing information from an RMP perspective. However, as this was originally a recommendation from the clinical evaluator, this matter was referred to the Delegate for consideration. The sponsor had also provided acceptable reasons for not aligning the summary of safety concerns with that of Ultibro Breezhaler except for the inclusion of 'use in pregnancy and lactation' as missing information. This was also referred to the Delegate for consideration. In response to the Delegate's overview, the sponsor has now included 'Asthma patients < 18 years and > 75 years' and 'Use in pregnancy and lactation' as missing information in the summary of safety concerns. The summary of safety concerns is now considered acceptable.
- The sponsor has proposed four different targeted follow-up checklists for ischemic heart disease/myocardial infarction, cardiac conduction abnormalities, acute and congestive heart failure, and stroke. This is considered acceptable from an RMP perspective.
- The sponsor has proposed routine risk minimisation activities through the proposed PI, Consumer Medicines Information (CMI); and Instructions for use (package insert) for the safety concern. This is satisfactory.

Risk-benefit analysis

Delegate's considerations

The evidence to support the proposed indication was based on the findings of a single pivotal study, Study CQVM149-B2302. The study met its primary endpoint (FEV_1), and did not achieve its key secondary endpoint (ACQ-7). Patients treated with both medium and high doses of QVM149 achieved statistically significant improvement in trough FEV_1, compared to corresponding doses of QMF149. The magnitude of improvement in FEV_1 was comparable across medium and high doses of QVM149 at Week 26 and 52. The Delegate has noted that FEV_1 as the chosen primary endpoint is not in line with the relevant EMA guidelines which recommend rate of exacerbations as the preferred primary endpoint for controller medications.[28] There was no significant improvement in quality of life measures such as ACQ-7 (key secondary endpoint) and AQLQ for patients treated with both medium and high doses of QVM149, compared to their corresponding doses of ICS/LABA.

Overall, a greater magnitude of reduction in the rate of exacerbations was reported with high dose QVM149 than the medium dose QVM149, when compared to corresponding doses of QMF149 and salmeterol/fluticasone. The clinical relevance of the magnitude of reduction in exacerbations with medium dose QVM149 (10% and 6% with all and severe exacerbations respectively), compared to medium dose QMF149 is unclear. Statistical significance was achieved only for the comparison of treatment difference in the reduction of exacerbations between the high dose QVM149 and high dose QMF149 and not with the

[28] EMA, CHMP, 22 October 2015. Guideline on clinical investigation of medicinal products in the treatment of Asthma (CHMP/EWP/2922/01 Rev.1).

medium doses of QVM149 and QMF149. The Delegate has considered that the study might not have been powered for such comparisons.

Clinical management of asthma is a targeted stepwise approach.[29] Medium dose ICS/LABA combination is the preferred controller for asthmatics with moderate disease severity (GINA Step 4).[30] LAMA, as a preferred controller and as an add-on to high dose ICS/LABA becomes a therapeutic option at GINA Step 5 for severe asthmatics.[30] Also, from a clinical perspective use of high dose ICS/LABA plus LAMA is targeted at 'difficult to treat and severe asthma' patients.[3] In the treatment paradigm of asthma, a LAMA (as a preferred controller) is considered as an add-on when there is inadequate asthma control for these patients after being treated with high dose ICS/LABA. If approved, the utility of high dose QVM149 will be for the treatment of these asthmatics with severe disease severity. The clinical utility of medium dose QVM149 in the treatment paradigm of asthma is unclear.

Tiotropium (a LAMA, approved by TGA for treatment of asthma and COPD) is currently Pharmaceutical Benefits Advisory Committee (PBAC) approved as an adjuvant therapy for the treatment of severe asthmatics, experiencing at least one exacerbation in the previous 12 months that required OCS treatment, in spite of treatment with a combination of LABA and high dose ICS.[31]

An increased incidence of dysphonia and cardiac events as treatment related adverse events were noted for patients treated with high dose QVM149, compared to medium dose QVM149. The cardiac events are known class effects of LABAs. The dose of LABA was identical for both medium and high doses of QVM149. Overall, the safety signals were in line with the known safety profile of the already registered monocomponents of QVM149. Treatment-related cardiac events are described well in the PI.

Proposed action

Treatment with both medium and high doses of QVM149 resulted in an improvement in lung function and measures of asthma control, when compared to respective QMF149 doses. The magnitude of improvement in lung function was statistically significant. However, it was not associated with a significant improvement in the measures of quality of life. Patients treated with the high dose QVM149 achieved greater reduction in exacerbations than medium dose QVM149 (compared to their corresponding doses of QMF149), which is a key objective of optimal asthma management.[32] The Delegate considers that the magnitude of the treatment effect (reduction in exacerbations) by the medium dose QVM149 may not be sufficient to translate to clinical significance. The clinical utility of medium dose QVM149 in the treatment paradigm of asthma is unclear. The treatment-related adverse effects are known class effects of LABAs, LAMAs and ICS. These are well described in the PI.

The Delegate considers that the evidence based on the data included in this submission indicates a positive benefit-risk profile for the high dose QVM149 for the proposed indication. The submitted data does not provide evidence to support the proposed use of the medium dose QVM149. The Delegate has recommended the following indication:

> *Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting*

[29] Papi, A. et al. Asthma, Lancet, 2018; 391(10122): 783-800.
[30] GINA. Global Strategy for Asthma Management and Prevention, 2020.
[31] Guide to Other Asthma Medicines (extracted from National Asthma Council, Australian Asthma Handbook website).
[32] Lommatzsch, M. and Virchow, J.C. Severe Asthma: Definition, Diagnosis and Treatment, Dtsch Arztebl Int, 2014; 111(50): 847-855.

beta2-agonist (LABA) and a high-dose of an inhaled corticosteroid (ICS), who experienced one or more asthma exacerbations in the previous year.

The further assessment of this submission will be based on sponsor's response to Delegate's PI recommendations and conditions of registration.

The Delegate suggested that the application for high dose Enerzair Breezhaler (150/50/160 μg) should be approved for registration.

The Delegate considers that the evidence based on the submitted data does not support the proposed use of the medium dose Enerzair Breezhaler (150/50/80 μg).

Question for sponsor

The Delegate has noted that the Enerzair Breezhalers that were approved in EU and Japan were equipped with a sensor. Please clarify whether the sponsor is planning to market a similar inhaler in Australia.

The Delegate rightfully pointed out that Enerzair Breezhaler high dose and Enerzair Breezhaler medium and high dose have respectively been approved in Europe and Japan together with a sensor. The sponsor would like to clarify that there currently is no intention to register nor market such a device in Australia.

Advisory committee considerations[33]

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.

Specific advice to the delegate

1. Based on the data in this submission, what are the ACM's views of approving the medium dose Enerzair Breezhaler (150/50/80 μg) for the treatment of asthma?

High dose Enerzair Breezhaler was recommended to be approved with the main reason being convenience for the patients. The target patient population would have already been on a triple therapy consisting of two inhalers. Their other options would be to progress to a biological agent, which is expensive, or increase the dose of ICS separately. The triple inhaler was not considered as a major breakthrough.

2. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM considered the definition of 'not adequately controlled' which could mean either: more than two exacerbations; zero exacerbations but waking up at night; needing to use Relievers, and so on. However, it is not within the scope of the ACM to define indications.

There is insufficient data to approve the medium dose of Enerzair Breezhaler. Even though the ACM agrees that low dose of ICS will result in the steroid sparing effect, the ACM's view

[33] 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.

of excluding the medium dose are that the studies were not designed for investigating steroid sparing or down titration. There were also no evidence for a clinically relevant treatment effect.

The ACM was of the view that the medium dose of Enerzair Breezhaler could be approved because it is demonstrated to be not worse than conventional treatment.

The ACM noted that there could be confusion of dose if Australia were to approve Enerzair's delivered dose to be printed on the device and packaging (the dose approved by the EU and Australia's TGO91 requirement) rather than the metered dose (the dose that are printed on inhalers in the market currently). For example the patient could be thinking they are getting less drug per puff. This issue could be resolved by education, and changing labels of other inhalers to display delivered dose, instead of metered dose.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Proposed (after first round of PI negotiation):

> *Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a LABA and an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.*

Delegate's recommended indication:

> *Enerzair Breezhaler 150(indacaterol)/50(glycopyrronium)/160(mometasone furoate) µg is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and a high-dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year*

The ACM agreed that Enerzair Breezhaler 150 (indacaterol)/ 50 (glycopyrronium)/ 80 (mometasone furoate) µg did not adequately demonstrate an overall beneficial profile for the proposed indication as the evidence submitted did not satisfactorily establish the efficacy of the product, in terms of reduction in exacerbations and quality of life measures.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Enerzair Breezhaler (indacaterol acetate/glycopyrronium/mometasone furoate) 114/46/136 µg and 114/46/68 µg powder for inhalation in capsule with inhaler, indicated for:

> *Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.*

Specific conditions of registration applying to these goods

- Enerzair Breezhaler (indacaterol acetate/glycopyrronium bromide/mometasone furoate) is to be included in the Black Triangle Scheme. The PI, CMI and Instructions for Use for Enerzair Breezhaler must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the products.
- The Enerzair Breezhaler EU-RMP, version 1.3, dated 21 April 2020 (DLP 14 June 2019), with ASA, version 1.1, dated 17 July 2020, included with submission PM-2019-

02514-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of RMP is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the EMA's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the DLP for that report.

Attachment 1. Product Information

The PI for Enerzair Breezhaler approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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