Australian Government
Department of Health
Therapeutic Goods Administration

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

Proprietary Product Name: Atectura Breezhaler

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

November 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
β_2AR	Beta 2 adrenergic receptor
β_2	Beta 2
100 PY	100 person years
ACM	Advisory Committee on Medicines
ACQ	Asthma Control Questionnaire
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
AusPAR	Australian Public Assessment Report
BID	Twice a day; Latin: *bis in die*
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
EMA	European Medicines Agency (European Union)
EU	European Union
FDC	Fixed dose combination(s)
FEV1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
LABA	Long-acting beta 2 agonist
LS	Least square
PI	Product Information
PK	Pharmacokinetic(s)
PSUR	Periodic Safety Update Report
QMF149	Drug development code for Atectura Breezhaler
RCT	Randomised control trial

Abbreviation	Meaning
SABA	Short-acting beta 2 (β_2) agonist
SAE	Serious adverse event
TGA	Therapeutic Goods Administration
UDDPI	Unit dose dry powder inhaler

I. Introduction to product submission

Submission details

Type of submission:	New fixed dose combination
Product name:	Atectura Breezhaler
Active ingredients:	Indacaterol (as acetate) and mometasone furoate
Decision:	Approved
Date of decision:	16 July 2020
Date of entry onto ARTG:	21 July 2020
ARTG numbers:	319074, 319075, 319076
, *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 Limited 54 Waterloo Road, Macquarie Park, NSW 2113
Dose form:	Inhalation powder in hard capsule
Strengths:	125 µg indacaterol/62.5 µg mometasone furoate 125 µg indacaterol/127.5 µg mometasone furoate 125 µg indacaterol/260 µg mometasone furoate
Container:	Inhaler
Pack sizes:	10 and 30 capsules
Approved therapeutic use:	*Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta$_2$-agonist and inhaled corticosteroid is appropriate:* • *patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists or*

[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.

- *patients not adequately controlled with long-acting beta$_2$-agonists and low dose of inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists*

Route of administration:	Inhalation
Dosage:	For adults and adolescents 12 years of age and older. Inhalation of the content of one capsule of Atectura Breezhaler 125/62.5 µg once daily is recommended in patients who require a combination of a long-acting β_2-agonist and a low dose of inhaled corticosteroid. Inhalation of the content of one capsule of Atectura Breezhaler 125/127.5 µg or 125/260 µg once-daily is recommended in patients who require a combination of a long-acting β_2-agonist and a medium or high dose of inhaled corticosteroid. The maximum recommended dose is Atectura Breezhaler 125/260 µg once daily. 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 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 Pharmaceutical Australia Pty Ltd (the sponsor) to register Atectura Breezhaler (indacaterol (as acetate)/mometasone furoate) 125 µg/62.5 µg; 125 µg/127.5 µg; 125 µg/260 µg inhalation powder in hard capsule for the following proposed indication:

Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta$_2$-agonist and inhaled corticosteroid is appropriate:

- *patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists or*

- *patients not adequately controlled with long-acting beta$_2$-agonists and low dose of inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists*

Asthma is a common disease affecting an estimated 340 million people worldwide.[2] Although asthma can develop at any age, it more commonly develops in childhood. According to the global asthma report;[2] asthma is has a higher occurrence in people aged 10 to 14 years and 75 to 79 years. In older adults, the prevalence of asthma is higher in the male population.[3] In Australia, 1 in 9 Australians have asthma (around 2.5 million); it is more common in males aged 0 to 14 years, but among those aged $\geq$ 15 years, asthma is more common in females. Deaths attributed to asthma have remained stable over the past 5 years at 1.5 deaths per 100,000 population with 421 people dying from asthma in 2015.[4] Asthma is associated with a poorer quality of life, with disease severity and the level of control both having an impact.

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 hyper-responsiveness and underlying inflammation. Asthma is a heterogeneous disease in its manifestations and also in its response to treatment and probably represents a spectrum of conditions with different pathophysiological mechanisms. In older patients, there may be substantial overlap with features of chronic obstructive pulmonary disease (COPD) and patients with an asthma / COPD overlap are at higher risk of exacerbations and complications. The diagnosis of allergic asthma is more likely when the person also has allergy and a family history of asthma.[5]

Previous versions of clinical guidelines for asthma classified '*asthma severity*' as intermittent, mild persistent, moderate persistent and severe persistent asthma based on clinical characteristics and medication required to maintain disease control. However recent guidelines define severity of asthma according to the treatment required to control symptoms and exacerbations. 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) + SABA as needed. Worldwide prevalence of mild asthma has been estimated at 3.3% and includes 50% to 75% of all asthmatic patients.[3]

The main objective in asthma treatment is to maintain asthma control. 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's (GINA) Global Strategy for Asthma Management and Prevention guidelines;[3] 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. GINA guidelines;[3] propose a classification of asthma severity by the type and intensity of controller medication required for the control of the disease (step 1 to 5) for investigational purposes. GINA guidelines; [3] also propose a classification in three categories (mild, moderate and severe asthma) assessed retrospectively once the patient is on regular controller treatment for several months. The stepwise approach to therapy, in which the dose and number of medications and

[2] The Global Asthma Report 2018. Accessible via globalasthmareport.
[3] 2020 GINA report, Global Strategy For Asthma Management and Prevention. Accessible via ginasthma.org.
[4] Statistics extracted from healthdirect.gov.au under section asthma statistics.
[5] Information extracted from asthmahandbook.org.au.

frequency of administration are increased as necessary and decreased when possible, is used to achieve and maintain asthma control.

The GINA guidelines;[3] 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) and long-acting β agonists. Relievers are medications used on an as needed basis to reverse bronchoconstriction and relieve symptoms (for example, short- and one long-acting beta 2 (β_2) agonists).

A long-acting beta 2 (β_2) agonist (LABA) plus ICS (LABA/ICS) is a well-established therapy class with a known safety profile. GINA guidelines;[3] define LABA/ICS as the cornerstone asthma therapy for GINA step 3 patients and above. The preferred treatment option for GINA step 3 asthma patients (adults and adolescents) is the combination of low dose LABA/ICS as maintenance treatment plus as SABA, or a combination low dose formoterol/ICS (budesonide or beclometasone) as both maintenance and reliever therapy.

The sponsor rationales that the concomitant administration of LABA and ICS plays an important role in the treatment of asthma. Most of the fixed dose combinations (FDC) of ICS and LABA are approved for twice a day (BID) regular treatment of asthma where use of a combination (LABA/ICS) is appropriate (for example, salmeterol/fluticasone propionate, formoterol fumarate/budesonide, formoterol/fluticasone propionate). Vilanterol/fluticasone furoate is the only approved LABA/ICS FDC for administration once daily. 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.[6]

QMF149;[8] is a once daily, fixed dose combination of a LABA and an ICS delivered by the Concept1Breezhaler device;[7] (also known asBreezhaler device), a unit dose dry powder inhaler (UDDPI).[8] The two individual components of QMF149;[8], indacaterol and mometasone furoate are widely authorised (including in European Union (EU) and Canada) as monotherapies or as combination products with other monotherapies for the treatment of either COPD or asthma. Indacaterol is a potent and nearly full agonist at the human beta 2 adrenoceptor (β_2AR) demonstrated to have a rapid onset of action (in isolated human bronchus), similar to salbutamol and formoterol. Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and anti-inflammatory properties. Studies in asthmatic patients have demonstrated that inhaled mometasone furoate provides a favourable ratio of pulmonary to systemic activity.[9,10] While there is clear evidence of lung function benefit as an expression of its anti-inflammatory primary pharmacodynamics, inhaled mometasone furoate is devoid of clinically relevant systemic steroid effects as expected from an inhaled drug with low oral bioavailability and low overall systemic exposure. Mometasone furoate is authorised as inhalation, nasal, cream, ointment and lotion formulations. The inhalation powder formulation is administered once daily. or BID. as a multi-dose dry powder inhaler (Twisthaler device) is widely authorised for the treatment of asthma in adults and adolescents ≥ 12 years of age.

Three strengths of QMF149;[8] are proposed for registration: QMF149 150/320 µg (LABA/high dose ICS); QMF149 150/160 µg (LABA/medium dose ICS); and QMF149 150/80 µg (LABA/low dose ICS). The range of doses will provide flexibility for physicians

[6] 2018 GINA report, Global Strategy For Asthma Management and Prevention. Accessible via ginasthma.org.
[7] Concept1Breezhaler device is the development code by sponsor for Breezhaler device.
[8] QMF149 is the drug development code used by sponsor for Atectura Breezhaler.
[9] Fausnight TB, Craig TJ (2011) Mometasone furoate dry powder inhaler for the treatment of asthma *Exp Opin Pharmacother*; 12(17):2702-12.
[10] Yang D, Wang J, Bunjhoo H, et al (2012) Comparison of the efficacy and safety of mometasone furoate to other inhaled steroids for asthma: a meta-analysis. *Asian Pac J Allergy Immunol*; 31(1):26-35.

to titrate ICS dose strengths accordingly to achieve asthma control which is in line with the step wise approach to asthma treatment outlined in the GINA guidelines.[6] A once daily regimen may also provide adherence benefits compared to bid regimen.

Regulatory status

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

At the time the TGA considered this application, a similar application had been approved in European Union (EU) on 30 May 2020, in Canada on 6 May 2020 and was under consideration in Switzerland.

Table 1 International regulatory status of Atectura Breezhaler

Region	Submission date	Status	Approved indications
EU	May 2019	Approved on 30 May 2020	*Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short-acting beta$_2$-agonists.*
Canada	22 May 2020	Approved on 06 May 2020	*Atectura Breezhaler is indicated as a maintenance treatment of asthma in adults and adolescents 12 years of age and older with reversible obstructive airways disease. Should be prescribed for patients not adequately controlled on a long-term asthma control medication, such as ICS or whose disease severity clearly warrants treatment with both a LABA and an ICS."*
Japan	30 July 2019	Approved on 29 June 2020	*"Bronchial asthma (in case requiring combination use of inhaled corticosteroids and inhaled long-acting β2-agonists)"*

Product Information

The 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-2019-02513-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2019
First round evaluation completed	10 February 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	15 June 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	16 July 2020
Completion of administrative activities and registration on the ARTG	21 July 2020
Number of working days from submission dossier acceptance to registration decision*	194

*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

The pharmaceutical chemistry evaluator has recommended approval of low, medium and high doses of QMF 149.[8] The evaluator has recommended to use the 'delivered dose' of mono components for labelling of the products. All outstanding quality, manufacturing and labelling issues have been resolved. Figures 1 and 2 (shown below) give the chemical structures of the indacaterol acetate and mometasone furoate components respectively.

Figure 1: Chemical structure of indacaterol acetate

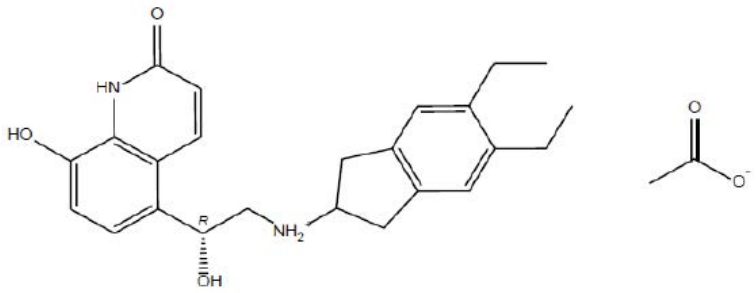
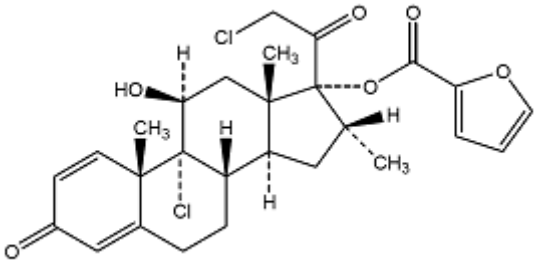


Figure 2: Chemical structure of mometasone furoate



QMF 149;[8] is formulated with micronized indacaterol acetate, micronized mometasone furoate and inhalation grade lactose encapsulated in a transparent hard gelatin capsule. The capsules are packaged in blister packs and the blister packs placed in cartons. The contents of the capsules are delivered to the patient's lungs using a unit dose dry powder inhaler known as the Breezhaler device.[7]

Nonclinical

There are no nonclinical objections to registration of Atectura Breezhaler.

Nonclinical dossier contained data on the primary pharmacology and repeat dose toxicity of the indacaterol acetate and mometasone furoate in combination, data comparing the pharmacokinetics (PK) and repeat dose toxicity of indacaterol acetate and indacaterol maleate, and an assessment of the mutagenic potential of actual and potential impurities of indacaterol.

A gene expression study in human bronchial epithelial cells, showing enhanced effects on the expression of a number of genes relevant to asthma with the combination compared with the single agents, offers support for the utility of the product in asthma. No PK interaction between the indacaterol and mometasone furoate was evident in rats and dogs.

Repeat dose toxicity studies of three months duration by the inhalational route in rats and dogs revealed no novel or notable additive toxicity with indacaterol acetate and mometasone furoate in combination. The acetate and maleate salts of indacaterol exhibited no difference in kinetics or toxicity in rats and/or dogs.

Pregnancy category B3,[11] as the sponsor proposes, is considered to be appropriate, based on reference to existing data for the individual components

[11] 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

All submitted toxicity studies were good laboratory practice compliant. The nonclinical dataset was adequate in scope, consistent with relevant TGA adopted guidelines.[12,13]

Clinical

The clinical dossier contained the following:

- four PK studies: Study CQMF149E2101, Study CQMF149E2102, Study CQVM149B2203 and Study CQMF149E1101;
- six pharmacodynamic studies: Study QMF149E2203, Study QVA149A2210, Study CQVM149B2203, Study CQAB149D2301, Study QMF149E2201 and Study CQAB149B2357;
- three Phase III trials: Study CQVM149B2301, Study CQVM149B2302 and Study CQVM149B2303;
- three supportive studies: Study CQVM149B1305, Study CQMF149A2210 and Study CQMF149F2202

Pharmacology

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

There were no clinically significant PK interactions between indacaterol acetate and mometasone furoate when administered as the proposed FDC.

Two Phase II studies (Study CQVM149B2203 and Study CQAB149D2301) demonstrated bioequivalence of indacaterol maleate and acetate salts following oral inhalation in asthma patients on background ICS.

A dose dependent treatment effect on trough forced expiratory volume in 1 second (FEV_1);[14] was observed following single doses of 37.5 µg, 75 µg and 150 µg indacaterol.

The mometasone furoate component of the FDC differed from the reference product Asmanex Twisthaler with regard to both the inhalation device and formulation delivered. A 3 step bridging approach was undertaken to identify doses of mometasone furoate administered via Concept1Breezhaler device;[7] comparable to those administered via the Twisthaler device. Variability in mometasone furoate exposure was reduced following administration via Concept1Breezhaler device;[7] compared with the Twisthaler device. The estimated average dose of mometasone furoate in Concept1Breezhaler;[7] expected to provide systemic exposure comparable to Twisthaler 400 µg was 195 µg. The fine particle mass corresponding to the nominal dose was determined, and based on these *in vitro* data, the doses of mometasone furoate 80 µg, 160 µg and 320 µg in the Concept1Breezhaler device;[7] were considered comparable to the approved mometasone furoate doses of 200 µg, 400 µg and 800 µg in the Twisthaler device respectively.

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.

[12] ICH M3 (R2): International Conference on Harmonisation (ICH) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals.

[13] EMEA/CHMP/SWP/258498/2005: European Medicines Evaluation Agency (EMEA) Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products.

Efficacy

The evidence of efficacy was provided in two Phase III studies in adults and adolescent patients with asthma.

Study CQVM149B2301

Study CQVM149B2301 was a 52-week, active-controlled randomised control trial (RCT) comparing the efficacy and safety of QMF149 150/160 µg (medium dose) and QMF149150/320 µg (high dose) delivered via Concept1Breezhaler device;[7] with corresponding doses of mometasone furoate (400 µg and 800 µg) delivered via Twisthaler device in patients with inadequately controlled asthma.

The primary and key secondary objectives were to demonstrate superiority of QMF149;[8] over mometasone furoate for trough FEV_1;[14] and on the Asthma Control Questionnaire-7 (ACQ-7);[15] at Week 26 of treatment period respectively.

There were multiple secondary endpoints including other lung function parameters, symptoms, rescue medication use and exacerbations. QMF149;[8] 150/320 µg versus salmeterol/fluticasone 50/500 µg BID as current approved standard of care was assessed as an additional secondary comparison.

Adult and adolescent patients with asthma for at least 1 year who were symptomatic (ACQ-7 score ≥ 1.5) on low dose ICS/LABA or medium to high dose ICS with pre-bronchodilator FEV_1;[16] ≥ 50 to < 85% predicted and qualified for medium to high dose ICS/LABA treatment were eligible to participate.

The study included 2216 randomised patients. Following 2 weeks run-in where patients received low dose ICS (fluticasone proprionate 100 µg BID or fluticasone low dose equivalent), patients were randomised in 1:1:1:1:1 ratio to 1 of 5 treatment arms:

- QMF149;[8] 150/160 µg via Concept1Breezhaler device;[7] once daily in the evening
- QMF149 150/320 µg via Concept1Breezhaler device once daily in the evening
- Mometasone furoate 400 µg via Twisthaler device once daily in the evening
- Mometasone furoate 800 µg (administered as 400 µg BID) via Twisthaler device
- Salmeterol xinafoate/fluticasone proprionate 50/500 µg BID via Accuhaler device

Demographics and baseline disease characteristics were generally balanced across treatment groups. The study population included 107 (4.8%) adolescents and 297 (13.4%) adults aged ≥ 65 years. Prior to the study, approximately 70% were treated with low dose ICS/LABA and 27% with medium or high dose ICS. Most patients (69.5%) did not have an exacerbation within the previous 12 months; 24.1% reported 1 exacerbation and 6.5% > 1 exacerbation. Mean ACQ-7 score was 2.30 at Baseline.

The majority of randomised patients completed 26 weeks of treatment.

The primary objective of the study was met, with superiority of both high and medium QMF149;[8] doses to corresponding mometasone furoate doses demonstrated. After 26 weeks of treatment, the estimated treatment difference in trough FEV_1;[14] was 0.130 L (95% confidence interval (CI): 0.086, 0.173; p < 0.001) for QMF149;[8] 150/320 µg versus

[14] Trough FEV1 is the mean volume of air that can be forced out in one second after taking a deep breath approximately 24 hours after the last administration of study drug.
[15] The **Asthma Control Questionnaire** (**ACQ-7**) has 7 questions (the top scoring 5 symptoms, FEV1% pred. and daily rescue bronchodilator use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0 = no impairment, 6 = maximum impairment).
[16] FEV1 is the amount of air patient can force from his/her lungs in one second.

mometasone furoate 800 µg and 0.211 L (95% CI: 0.167, 0.255; p < 0.001) for QMF149 150/160 µg versus mometasone furoate 400 µg.

Non-inferiority of QMF149;[8] 150/320 µg to salmeterol /fluticasone 50/500 µg was demonstrated.

Subgroup analysis by age showed improvements in trough FEV_1;[14] for adolescents were comparable to those for adults.

The key secondary objective was met; after 26 weeks of treatment, the least square (LS) of the mean;[17] treatment difference in ACQ-7;[15] score for pooled QMF149;[8] versus pooled mometasone furoate was 0.209 (95% CI: 0.270, 0.148, p < 0.001).

There were 76.3% patients in the pooled QMF149;[8] group and 69.7% patients in the pooled mometasone furoate group who were responders (improvement in ACQ-7 score from Baseline by the minimal clinically important difference of ≥ 0.5 units); odds ratio 1.51 (95% CI: 1.21, 1.89).

The proportion of patients with exacerbations was lower in the QMF149;[8] treatment groups than the mometasone furoate treatment groups. The rate of moderate or severe exacerbations was reduced for both QMF149;[8] 150/320 µg versus. mometasone furoate 800 µg (rate ratio 0.60; 95% CI: 0.43, 0.83) and QMF149;[8] 150/160 µg versus. mometasone furoate 400 µg (rate ratio 0.49; 95% CI: 0.36, 0.68). The reduction in the rate of moderate or severe exacerbations was similar for QMF149;[8]150/320 µg and salmeterol/ fluticasone 50/500 µg.

Secondary endpoints relating to other lung function parameters, symptoms, rescue medication use and quality of life scores were supportive.

Week 52 data were provided by the sponsor at the second round of evaluation; efficacy results observed at Week 26 were maintained. Similar trends in the rate of exacerbations were observed.

Study CQVM149B2303

Study CQVM149B2303 was a 12-week RCT comparing the efficacy and safety of low dose QMF149;[8] 150/80 µg via Concept1Breezhaler device;[7] with mometasone furoate 200 µg via Twisthaler device in patients with inadequately controlled asthma. The primary and key secondary objectives were identical to Study CQVM149B2301 and assessed after 12 weeks of treatment.

Adult and adolescent patients with asthma for at least 3 months who were symptomatic (ACQ score ≥ 1.5 for all adults and those adolescents on ICS, ≥ 1 and < 1.5 for adolescents on ICS/LABA) who qualified for treatment with low dose ICS/LABA were eligible to participate.

Following a 3 weeks run-in with low dose fluticasone propionate, patients were randomised in 1:1 ratio to QMF149;[8] 150/80 µg or mometasone furoate 200 µg.

The study included 802 randomised patients, with 768 (95.8%) completing study treatment.

Baseline demographics and disease characteristics were comparable between the two treatment groups. The study population included 64 (8.0%) adolescents and 108 (13.5%) adults aged ≥ 65 years. There were 42.9% on low dose ICS and 56.0% on low dose ICS/LABA. In the 12 months prior to screening, 80.2% patients did not have an exacerbation. The mean ACQ-7 score was 2.27 at Baseline.

[17] Least square means are means for groups that are adjusted for means of other factors in the model.

QMF149;[8] 150/80 µg demonstrated superiority over mometasone furoate 200 µg for the primary endpoint. After 12 weeks of treatment the LS mean treatment difference (QMF149 versus mometasone furoate) for trough FEV_1;[14] was 0.182 L (95% CI: 0.148, 0.217; $p < 0.001$). Subgroup analysis by age showed similar improvements in trough FEV_1 for adolescent and adult patients.

For the key secondary endpoint ACQ-7;[15] there was a statistically significant treatment difference (QMF149;[8] versus. mometasone furoate) after 12 weeks of 0.218 (95% CI: 0.293, 0.143). There were 74.7% patients in the QMF149;[8] 150/80 µg group and 64.9% patients in the mometasone furoate 200 µg group who were responders at 12 weeks; odds ratio 1.69 (95% CI: 1.23, 2.33).

Secondary endpoints of lung function, symptoms and rescue medication use were in favour of QMF149;[8] 150/80 µg. The study duration is too short to draw any conclusions in terms of treatment effects on exacerbation rate.

Safety

The 1-year safety database included pooled data from Studies CQVM149B2301, CQVM149B2303 and CQVM149B2302. The study population included adult patients with severe asthma poorly controlled on medium and high dose ICS/LABA (GINA step ≥ 4);[3] with at least 1 exacerbation within the previous year.

The evaluator considered pooling of the studies was acceptable, and noted the safety results from the individual Phase III studies were consistent with the pooled analyses.

The overall occurrence rate of adverse events (AE) was lower in the QMF149;[8] groups compared with the corresponding mometasone furoate groups or salmeterol/fluticasone 50/500 group (QMF149 all doses versus mometasone furoate all doses = 207.6 versus 268.6 per 100 person-years (100 PY), QMF149 medium + high dose versus mometasone furoate medium + high dose = 206.8 versus. 265.5 per 100 PY, QMF149 high dose versus salmeterol/fluticasone 50/500 = 237.7 versus. 283.5 per 100 PY).

Some of the common AEs (asthma, nasopharyngitis, upper respiratory tract infection) occurred less frequently in the QMF149;[8] groups, whilst dysphonia occurred more frequently in the QMF149 groups compared to the mometasone furoate groups (2.1 to 2.5 versus 0.9 to 1.1 per 100 PY), and at a similar rate for QMF149 high dose and salmeterol/fluticasone 50/500 (2.2 versus 1.8 per 100 PY).

The majority of AEs were mild or moderate in severity and generally comparable across groups. Severe AEs were less common in the QMF149;[8] groups (18.3 to 36.0 per 100 PY) versus comparators (32.6 to 45.5 per 100 PY), with asthma (exacerbation) the most frequently reported severe AE.

The occurrence rates for AEs suspected to be related to study treatment were slightly lower in QMF149;[8] groups (10.5 to 12.7 per 100 PY) versus corresponding comparators (14.2 to 15.2 per 100 PY). The most common treatment-related AEs were asthma (exacerbation) and dysphonia.

AEs leading to discontinuation of study medication were lower in the QMF149;[8] groups (1.8 to 3.5 per 100 PY) versus other comparators (4.8 to 5.6 per 100 PY). Asthma (exacerbation)-was the most common reason for discontinuation overall, with the occurrence rate of all other AEs leading to discontinuation of study drug ≤ 0.4 per 100 PY. There were no discontinuations in the QMF149 groups due to asthma.

The occurrence rate of serious adverse events (SAEs) was lower in the QMF149;[8] groups (6.9 per 100 PY) versus the corresponding mometasone furoate groups (9.1 to 9.5 per 100 PY) and slightly higher in the QMF149 high dose group (10.7 per 100 PY) versus the salmeterol/fluticasone 50/500 group (8.9 per 100 PY). The most frequently reported SAEs

were asthma and pneumonia, both occurring less frequently in QMF149 groups versus corresponding mometasone furoate comparators.

There was one adjudicated asthma related death in the mometasone furoate medium dose group. Adjudicated asthma related hospitalisation was numerically higher in the QMF149;[8] high dose group (1.7 per 100 PY) than the salmeterol/fluticasone 50/500 group (1.0 per 100 PY).

There were four deaths in the QMF149;[8] high dose group in Study CQVM149B2302 (n = 2 sudden cardiac death, n = 1 cancer (lymphoma), n = 1 accidental death (train accident)) and 1 death due to status asthmaticus in the mometasone furoate medium dose group occurring on Day 314 in Study CQVM149B2301 as noted above; none of the deaths were considered related to study treatment.

Adverse events of special interest based on known class effects of LABA and ICS are shown below.

Table 3: All adverse events of special interest by risk category adjusted for exposure, by risk

Risk (special interest AE)	QMF149 medium+high N=880 exp=777.4 m (OccR)	MF medium+high N=883 exp=766.2 m (OccR)	QMF149 all N=1276 exp=868.6 m (OccR)	MF all N=1282 exp=857.1 m (OccR)	QMF149 high N=1056 exp=916.0 m (OccR)	S/F 50/500 N=1062 exp=921.1 m (OccR)
Bladder obstruction and urinary retention	0	2 (0.3)	0	3 (0.4)	1 (0.1)	1 (0.1)
Bone Fracture	9 (1.2)	9 (1.2)	10 (1.2)	14 (1.6)	16 (1.7)	9 (1.0)
CCV events: Any category	30 (3.9)	28 (3.7)	32 (3.7)	30 (3.5)	48 (5.2)	39 (4.2)
CCV events: Cardiac arrhythmia terms *: Atrial Fibrillation	3 (0.4)	5 (0.7)	3 (0.3)	6 (0.7)	7 (0.8)	8 (0.9)
CCV events: Cardiac arrhythmia terms *: Bradyarrhythmia	0	1 (0.1)	0	1 (0.1)	0	0
CCV events: Cardiac arrhythmia terms*: Cardiac arrhythmia terms, nonspecific	0	0	1 (0.1)	0	0	0
CCV events: Cardiac arrhythmia terms *: Cardiac repolarization abnormalities	4 (0.5)	3 (0.4)	4 (0.5)	4 (0.5)	2 (0.2)	3 (0.3)
CCV events: Cardiac arrhythmia terms *: Conduction abnormalities	6 (0.8)	1 (0.1)	7 (0.8)	1 (0.1)	5 (0.5)	3 (0.3)
CCV events: Cardiac arrhythmia terms *: Ectopics	1 (0.1)	4 (0.5)	1 (0.1)	4 (0.5)	5 (0.5)	6 (0.7)
CCV events: Cardiac arrhythmia terms *: Tachyarrhythmias	4 (0.5)	2 (0.3)	4 (0.5)	2 (0.2)	11 (1.2)	5 (0.5)
CCV events: Cardiac arrhythmia terms: Sudden death and sudden cardiac death	0	0	0	0	1 (0.1)	0
CCV events: Cerebrovascular events	2 (0.3)	4 (0.5)	2 (0.2)	4 (0.5)	6 (0.7)	9 (1.0)
CCV events: Ischaemic heart disease	8 (1.0)	8 (1.0)	8 (0.9)	8 (0.9)	7 (0.8)	3 (0.3)
CCV events: Myocardial infarction	2 (0.3)	0	2 (0.2)	0	5 (0.5)	2 (0.2)
Cataract	3 (0.4)	1 (0.1)	3 (0.3)	1 (0.1)	4 (0.4)	0
Diabetes mellitus/ hyperglycaemia	20 (2.6)	17 (2.2)	23 (2.6)	19 (2.2)	30 (3.3)	25 (2.7)
Glaucoma/increased intraocular pressure	1 (0.1)	0	1 (0.1)	0	1 (0.1)	0
Hypercorticoidism and adrenal suppression	0	0	0	0	0	1 (0.1)
Hypersensitivity	437 (56.2)	740 (96.6)	475 (54.7)	826 (96.4)	716 (78.2)	918 (99.7)
Hypokalaemia	0	2 (0.3)	0	2 (0.2)	0	1 (0.1)
Immunosuppression	58 (7.5)	84 (11.0)	62 (7.1)	94 (11.0)	102 (11.1)	141 (15.3)
Intubation, hospitalization and death due to asthma related events in asthma population	4 (0.5)	14 (1.8)	5 (0.6)	15 (1.8)	17 (1.9)	11 (1.2)
Liver toxicity	15 (1.9)	28 (3.7)	18 (2.1)	33 (3.9)	17 (1.9)	18 (2.0)
Medication error: Device interchangeability or Swallowing of capsules	2 (0.3)	8 (1.0)	8 (0.9)	22 (2.6)	1 (0.1)	2 (0.2)
Paradoxical bronchospasm	0	6 (0.8)	0	6 (0.7)	0	1 (0.1)
QTc prolongation and interaction with drugs known to prolong QTc interval	4 (0.5)	3 (0.4)	4 (0.5)	4 (0.5)	2 (0.2)	3 (0.3)
Reduced bone mineral density	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)	4 (0.4)	3 (0.3)

Conduction abnormalities and tachyarrhythmia were more common in the high dose QMF149;[8] group than all of the mometasone furoate and salmeterol/fluticasone groups.

There were 2 SAEs of myocardial infarction in the QMF149;[8] medium + high dose group; both patients had cardiovascular comorbidities. The events resolved without sequelae. Ischaemic heart disease was more common in the QMF149 high dose group versus salmeterol/fluticasone 50/500 µg. Two events in the QMF149 high dose group were SAEs and 1 event was fatal. There were five episodes of myocardial infarction in the QMF149 high dose group (versus 2 episodes in the salmeterol/fluticasone 50/500 µg group); cardiovascular comorbidities were present for 3 of these 5 patients.

Hyperglycaemia AEs were generally comparable across all treatment arms. There were no hypokalaemia AEs in the QMF149;[8] treatment groups.

Overall, serious adverse events of special interest were lower in QMF149;[8] groups (2.0 to 2.1 per 100 PY) versus corresponding mometasone furoate comparators (5.2 to 5.5 per 100 PY), whilst slightly higher in the QMF149 high dose group versus the salmeterol/fluticasone 50/500 µg group (5.2 versus 4.0 per 100 PY).

There were no major imbalances across the treatment groups with regard to laboratory parameters, electrocardiogram (ECG) findings or vital signs.

AE profiles were generally similar for adults and adolescents. Longer exposure is required to assess any potential effects on growth, however it is noted there were no AEs related to growth reported in the 52 week clinical study report for Study CQVM149B2301.

The evaluator did not identify any additional safety concerns in the 52 week safety data provided at the second round of evaluation.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[18]

The clinical evaluator considered the summary of safety concerns was acceptable however stated there is missing information in asthma patients < 12 years and > 75 years.

Risk-benefit analysis

Delegate's considerations

Studies CQVM149B2301 and CQVM149B2303 provided the efficacy and safety data for each of the proposed strengths of QMF149.[8] The primary endpoint was met in both studies. The between group treatment differences were above the accepted clinically meaningful difference of 0.1 L, ranging from 0.130 L to 0.211 L for each comparison. The medium dose QMF149 achieved a *greater treatment difference* in FEV_1 (211 mL) than high dose QMF149 (130 mL), when compared to corresponding doses of mometasone furoate.

The key secondary endpoint was met in both studies. Whilst both results were statistically significant, the between group differences were smaller than the accepted clinically meaningful difference in ACQ-7 of at least 0.5.

The baseline clinical characteristics of patients in both clinical Studies CQVM149B2301 and CQVM149B2303 were not representative of the asthmatics who will potentially be treated with the three proposed strengths of Atectura Breezhaler inhalers. In Study CQVM149B2301, 70% of patients did not experience an exacerbation in the 12 months preceding to screening. In clinical practice, these patients would not have been up-titrated to medium or high dose ICS/LABA. Similarly, in Study CQVM149B2303, 56% of

[18] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

patients were already on low dose ICS/LABA at Baseline and 80% of patients did not experience an exacerbation in the 12 months prior to screening.

The proportion of patients who experienced mild, moderate and severe asthma exacerbations during treatment period was lower in patient groups treated both medium and high doses of QMF149;[8] compared to corresponding doses of mometasone furoate and salmeterol/fluticasone groups. However, there was *no major difference* in the proportion of patients in high dose QMF149 group with exacerbations during study period, compared to medium dose QMF149 (22.8 (high dose) versus 24.7 (medium dose)). This could be attributed to the low exacerbation rate at Baseline and the dose-response relationship for ICS treatment effect on exacerbation rate (ceiling effect).

The relevant European Medicines Agency (EMA) guideline;[19] recommends exacerbations as the preferred endpoint for a new controller treatment. Lung function is recommended to be '*measured either as a co-primary or a key secondary endpoint*'. From a clinical perspective, '*controller medications*' such as ICS/LABA FDC are used in the treatment paradigm of asthma to achieve reduction in exacerbations, which is an important determinant of asthma control. It was noted that the proposed indication does not mention prevention/reduction of asthma exacerbations.

The efficacy of low dose QMF was not compared against an active comparator. The EMA guideline;[20] or asthma medications recommend '*an active comparator trial for a drug that is intended as a first-line controller treatment'.* For this comparison, the guideline;[20] recommends that the inhaled corticosteroid should be given in an '*adequate dose and for an adequate duration'*. It was noted that the duration of the Study CQVM149B2303 was 12 weeks. This duration is shorter than the recommended duration of 24 weeks;[19] for controller medication to demonstrate efficacy in terms of reduction in exacerbations, which is the main purpose of use of ICS/LABA FDC in asthma management. The Delegate has noted that the patients in the QMF149;[8] group achieved a significant improvement in FEV_1 and ACQ-7 after 12 weeks of treatment period.

Exposure to medium and high dose QMF149;[8] was adequate to assess safety. Treatment exposure to low dose QMF149 was 12 weeks, which is inadequate to assess safety. The 52 weeks duration of Study CQVM149B2301 provided safety data of medium and high doses of QMF149. Overall, the type of safety signals reported in patients treated with QMF149 was consistent with the known safety profile of ICS and LABA, with no new safety signals identified.

Greater proportion of patients treated with high dose QMF149;[8] experienced cardiac events such as tachyarrhythmias and conduction abnormalities, compared to those treated with medium dose QMF149, or the mometasone furoate and salmeterol/fluticasone groups. A greater incidence of ischemic heart disease was also reported in the high dose QMF149 group, compared to salmeterol/fluticasone group. The cardiac events are related to the LABA component. It was noted that the dose of indacaterol (LABA) was the same in both medium and high doses of QMF149.

Overall, the clinical evaluator considered the benefit-risk balance for QMF149;[8] as favourable.

[19] EMA/CHMP Guideline on clinical investigation of medicinal products in the treatment of Asthma (October 2015).
[20] CHMP 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 (22 January 2009)

Proposed action

Both medium and high doses of QMF149;[8] achieved greater improvement in lung function, ACQ scores and greater reduction in exacerbations, compared to corresponding doses of mometasone furoate and salmeterol/fluticasone. The low dose QMF149 also achieved these endpoints, compared to corresponding dose of mometasone furoate.

In clinical practice, a targeted approach is taken for maintenance therapy of asthma. The Delegate has considered the wider options that prescribers might get if the low, medium and high doses of ICS in QMF149;[8] are approved. There was an increased incidence of dysphonia and cardiac safety signals with high dose QMF149 when compared to medium dose QMF149. These are known treatment related adverse events and class effects with ICS and LABA respectively. Cardiac effects of LABA have been described adequately in the PI.

Further assessment of this submission will be based on sponsor's response to recommended changes to PI.[21]

Advisory Committee considerations[22]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Atectura Breezhaler 125 µg indacaterol/62.5 µg mometasone furoate; 125 µg indacaterol/127.5 µg mometasone furoate; 125 µg indacaterol/260 µg mometasone furoate powder for inhalation in hard capsule with inhaler, indicated for:

> *Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta$_2$-agonist and inhaled corticosteroid is appropriate:*
>
> - *patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists or*
> - *patients not adequately controlled with long-acting beta$_2$-agonists and low dose of inhaled corticosteroids and 'as needed' inhaled short-acting beta$_2$-agonists*

Specific conditions of registration applying to these goods

- Atectura Breezhaler (indacaterol acetate and mometasone furoate) is to be included in the Black Triangle Scheme. The PI and CMI for Atectura Breezhaler must include the

[21] Sponsor clarification, all recommended changes to PI have been resolved prior to approval of Atectura Breezhaler.

[22] 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.

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.

- This approval does not impose any requirement for the submission of Periodic Safety Update Reports (PSUR). It should be noted that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The PI for Atectura 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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