Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Beclometasone dipropionate/ formoterol fumarate/ glycopyrronium bromide

Proprietary Product Name: Trimbow

Sponsor: Emerge Health 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_2	Beta 2
AATD	Alpha-1 antitrypsin deficiency
AC	Adjudication Committee
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-Specific Annex
AUC	Area under the serum concentration time curve
$AUC_{0-\tau}$	Area under the serum concentration time curve from time 0 to the last measurable concentration
AUC_{0-12}	Area under the serum concentration time curve from time 0 to 12 hours
B17MP	Beclometasone-17-monopropionate
BID	Twice daily (Latin: *bis in die*)
CAT	Chronic obstructive pulmonary disease assessment test
CHF 1535	Drug development code name for Fostair
CHF 5993	Drug development code name for Trimbow
CI	Confidence interval
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
DPI	Dry-powder inhaler
ECG	Electrocardiogram
EU	European Union
FDC	Fixed dose combination

Abbreviation	Meaning
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GMR	Geometric mean ratio
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
ICS	Inhaled corticosteroid
IP	Intraperitoneally
IV	Intravenous
ITT	Intention-to-treat
LABA	Long-acting beta 2 (β_2)agonist
LAMA	Long-acting muscarinic antagonist
MACE	Major adverse cardiovascular event
OD	Once daily
PI	Product information
PK	Pharmacokinetic(s)
pMDI	Pressurised metered dose inhaler
PO	Orally (Latin: *per os*)
PP	Per protocol
PSUR	Periodic safety update report
QT	Time interval between the Q and T waves
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RCT	Randomised controlled trial
RR	Relative risk
RMP	Risk management plan
SABA	Short acting beta 2 (β_2) agonist

Abbreviation	Meaning
SAE	Serious adverse event
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
TDI	Transition dyspnoea index
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New combination of active ingredients
Product name:	Trimbow
Active ingredients:	Beclometasone dipropionate/ formoterol (eformoterol) fumarate dihydrate/ glycopyrronium bromide (glycopyrrolate)
Decision:	Approved
Date of decision:	18 June 2020
Date of entry onto ARTG:	24 June 2020
ARTG number:	314166
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Emerge Health Pty Ltd Suite 3/ 22 Gillman Street Hawthorn east, Vic 3123
Dose form:	Pressurised inhalation solution
Strength:	Fixed dose combination of 100 µg beclometasone dipropionate beclometasone dipropionate, 6 µg formoterol (eformoterol) fumarate formoterol fumaratedihydrate and 12.5 µg glycopyrronium bromide (glycopyrrolate)glycopyrronium bromide
Container:	Pressurised container with a metering valve
Pack size:	One (120 actuations)
Approved therapeutic use:	*Trimbow is indicated for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta2-agonist (LABA) or a combination of a LABA and a long-acting muscarinic antagonist (LAMA)*
Route of administration:	Inhalation

[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.

Dosage:	The recommended dose is two inhalations of Trimbow (beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide 100 µg/6 µg/12.5 µg) twice daily. The patient should take two inhalations in the morning and two inhalations in the evening at the same time every day. 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 Emerge Health Pty Ltd (the sponsor) to register Trimbow (beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide 100 µg/6 µg/12.5 µg, inhalation, pressurised) for the following proposed indication:

> *Trimbow is indicated for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta2-agonist (LABA) or a combination of a LABA and a long-acting muscarinic antagonist (LAMA).*

Chronic obstructive pulmonary disease (COPD) is a major public health problem and is the fourth leading cause of death in the world.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) document;[2] defines COPD as '*a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*'.

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches. According to World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD worldwide.[3] Globally, the prevalence of COPD increases with smoking status. More than

[2] Global strategy for the diagnosis management, and prevention of chronic obstructive pulmonary disease 2018 report. Available from goldcopd.org.
[3] Available from who.int website; information extract from section burden of COPD burden.

3 million people died of COPD worldwide in 2012, which is equal to 6% of all deaths globally that year.[2] The projection for 2020 indicates that COPD will be the third leading cause of death worldwide.[2] The major risk factor for COPD is cigarette smoking, however, all of the following are considered to be risk factors for COPD: occupational airborne exposure; outdoor and indoor pollution; socioeconomic status; early life environmental factors (for example, smoking mothers, frequent respiratory infections and asthma in childhood etc.); genetic factors (for example, hereditary deficiency of α-1-antitrypsin (AATD)); age; gender; lung growth and development; infections; asthma; chronic bronchitis. A recent meta-analysis showed that female smokers experience a faster decline in lung function after the age of 45 years compared with male smokers.[4]

Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD. The mainstays of treatments for symptomatic relief in stable COPD are bronchodilators and, as the disease worsens, inhaled corticosteroids (ICS) and phosphodiesterase 4-inhibitors as anti-inflammatory agents are recommended in combination with long-acting bronchodilators. The main classes of bronchodilators used in COPD are beta 2 (β_2)-agonists and anti-cholinergic agents. Short acting β_2-agonists (SABA; for example, salbutamol, terbutaline and fenoterol) are used for acute bronchodilation and relief of symptoms. Long acting β_2 agonists (LABA; for example, salmeterol, formoterol and indacaterol) exhibit a prolonged duration of effect of 12 hours or more, and are used to achieve more sustained symptom control. Anti-cholinergics (for example, the short-acting ipratropium bromide, and the long acting glycopyrronium bromide glycopyrronium bromide and tiotropium) exert their effect by blocking the effect of acetylcholine on the muscarinic receptors on the airway smooth muscles. Additional important non-pharmacologic components of the management of COPD include physical exercise, pulmonary rehabilitation and oxygen therapy. Invasive/surgical treatments including bronchoscopic lung volume reduction, lung transplantation and bullectomy may be appropriate in selected patients.

The CHF 5993 pressurised metered dose inhaler (pMDI);[5] is a fixed dose combination (FDC) of the ICS beclometasone dipropionate, the LABA formoterol fumarate and the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide. This FDC is denoted by the sponsor's product code CHF 5993 pMDI with a nominal dose per actuation of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide of 100 µg, 6 µg and 12.5 µg, respectively, formulated as a hydrofluoroalkane (HFA) solution to be delivered via a pMDI.

The clinical rationale as stated by the sponsors is as follows:

> 'In line with the FDC guidelines,[6] the development of CHF 5993 pMDI;[5] in COPD was based on the potential advantage of obtaining the following:
>
> - An improvement of the benefit/risk by demonstration of better efficacy of CHF 5993 pMDI[5] versus CHF 1535 pMDI (beclometasone dipropionate/formoterol fumarate combination);[7] with a similar acceptable safety profile;
> - A simplification of the therapy, as the three active components are administered with one dose regimen twice daily (BID) in a single inhaler, whereas the current triple therapy is often achieved with two different inhalers usually at two different

[4] Gan, W. Q. et al. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respiratory research, 2006, 7(1), 52.
[5] CHF 5993 pressurised metered dose inhaler (pMDI) is the drug development code used by sponsor for Trimbow.
[6] European Medicines Agency (EMA), Committee for Human Medicinal Products (CHMP), Guideline on clinical development of fixed combination medicinal products, EMA/CHMP/158268/2017, 23 March 2017.
[7] CHF 1535 pMDI (beclometasone dipropionate / formoterol fumarate combination) is drug development code used by sponsor for Fostair pressurised inhalation solution (AUST R 310360).

dose regimens (BID for the ICS/LABA combination and once daily (OD) for the LAMA component) (so-called free triple).

In addition, as a result of the extrafine product characteristics (for example, mass median aerodynamic diameter of around 1.1 µm and high fine particle dose), CHF 5993 pMDI;[5] is characterised by a reduced ICS dose and a more homogeneous (central and peripheral) lung deposition compared to existing non-extrafine inhaled therapies, with a fast onset of bronchodilation and reduced systemic exposure to the drug.

Therefore, CHF 5993 pMDI;[5] could ease the burden of using multiple inhalers while potentially improving patients' adherence and allowing better treatment compliance.'

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 (approved on 29 September 2016), Mexico (approved on 14 November 2017), Turkey (approved on 6 December 2017), Albania (approved on 26 June 2018), Kosovo (approved on 27 September 2018) and was under consideration in 13 other countries/regions.

Table 1: International regulatory status of Trimbow

Region	Submission date	Status	Approved indications
European Union	29 September 2016	Approved on 17 July 2017	*Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long acting muscarinic antagonist*
Mexico	14 November 2017	Approved on 15 February 2018	*Symptomatic treatment and reduction of exacerbations in adult patients with chronic obstructive pulmonary disease (COPD) GOLD Stage C and D who are at risk for exacerbations:* • *Not adequately controlled with inhaled combination of corticosteroids and bronchodilators, or with bronchodilators alone; or* • *Eligible for treatment with inhaled corticosteroids, longacting β2-agonists and long acting muscarinic antagonists.*

Region	Submission date	Status	Approved indications
Turkey	6 December 2017	Approved on 15 September 2018	*Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist.*
Albania	15 May 2018	Approved on 26 June 2018	*Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist.*
Kosovo	6 June 2018	Approved on 27 September 2018	*Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist.*

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-2019-00405-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	10 May 2019
First round evaluation completed	6 February 2020
Sponsor provides responses on questions raised in first round evaluation	14 April 2020
Second round evaluation completed	22 April 2020
Delegate's Overall benefit-risk assessment	20 May 2020
Sponsor's pre-Advisory Committee response	Not applicable

Description	Date
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	18 June 2020
Completion of administrative activities and registration on the ARTG	24 June 2020
Number of working days from submission dossier acceptance to registration decision*	155

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

Quality

There were no objections to registration from the quality evaluator.

Trimbow is a pMDI containing 100 µg/actuation of beclometasone dipropionate, 6 µg/actuation of formoterol fumarate and 12.5 µg/actuation of glycopyrronium bromide in an ethanolic solution, propelled by HFA-134a (norflurane) delivering nominally 120 actuations/canister.

The structure of beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium bromide are shown below.

Figure 1: Structure of beclometasone dipropionate

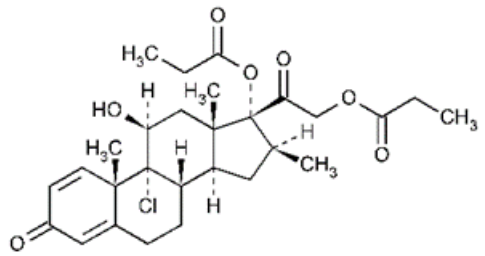


Figure 2: Structure of formoterol fumarate dehydrate

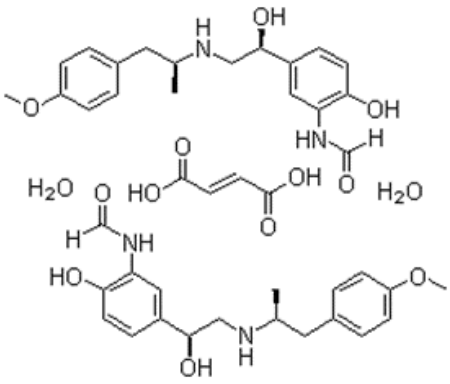
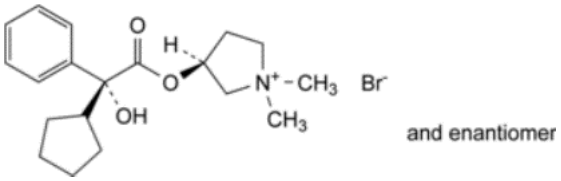


Figure 3: Structure of glycopyrronium bromide



The primary container for the inhalation solution is an aluminium coated pressurised canister fitted with a 63 µL metering valve, using a polypropylene actuator for inhalation and an integrated (in the actuator) with a dose counter system.

The shelf life for Trimbow is 18 months when stored between 2 to 8°C plus a maximum of 2 months in-use period (from dispensing) when stored below 30°C.

Nonclinical

There were no objections to the registration from the nonclinical evaluator.

The following conclusions were made in the nonclinical evaluation report:

- Additive inhibition of bronchoconstriction and inflammatory changes was demonstrated for the triple combination *in vivo* in studies in normal or sensitised guinea pigs.
- Safety pharmacology studies with the triple combination revealed effects on cardiovascular and respiratory parameters in dogs, as expected from the pharmacological actions of the LABA and LAMA components.
- No pharmacokinetic (PK) interaction between the three components was apparent in rats and dogs. Based on in vitro potency data, no clinically relevant inhibition of transporters to give rise to pharmacokinetic interactions in patients is predicted.
- A low order of acute toxicity was evident for the triple combination by the oral (PO) and intraperitoneal (IP) routes in single-dose studies in rats.
- Repeat-dose inhalational toxicity studies of 3 months duration revealed no novel or notable exacerbation of toxicity with the triple combination in rats and dogs. Major findings reflected exaggerated pharmacological effects. As expected, in dogs, the addition of glycopyrronium bromide led to more pronounced electrocardiogram (ECG) changes compared with that seen with beclometasone dipropionate and formoterol fumarate in dual combination.
- Reproductive and developmental toxicity was observed with the triple combination in rats. Findings included impairment of fertility, inhibition of ovulation, increased pre- and post-implantation loss, dystocia, decreased fetal/pup weight, increased fetal visceral variations, impaired fetal ossification, decreased perinatal survival and reduced reproductive function of the offspring. These findings are principally attributable to beclometasone dipropionate, and mostly occurred at extremely large multiples of the clinical exposure to the corticosteroid component of Trimbow. The tocolytic effect is due to formoterol fumarate as a β_2-adrenoceptor agonist, and occurred in animals at formoterol exposure levels lower than in patients. Assignment to pregnancy category B3;[8] is recommended.

[8] 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.

Clinical

The clinical dossier consisted of:

- Two PK studies in healthy subjects
- Three PK studies in target patient population (Studies Triple 4, Glyco 2 and CARSAF)
- One study in patients with renal impairment (Study Triple 10)
- Two drug interaction studies (Studies Triple 1 and Triple 12)
- Three population PK analyses (RP-0006, RP-0004 and RP-0005)
- Three Phase II studies (Studies Glyco 2, Triple 3 and CARSAF)
- One Phase IIb (Study Triple 9).
- Two Phase III clinical studies (Studies Triple 5 and Triple 6)
- Two Phase IIIb clinical studies (Studies Triple 7 and Triple 8).
- Post-marketing safety data is provided as a periodic safety update report (PSUR), covering the period of 17 July 2017 to 16 January 2018.

Pharmacology

A summary of the pharmacology studies is shown in Table 3.

Table 3: Summary of the pharmacology studies

Study name	Description	Findings
Triple 2	Compared the bioavailability of 4 actuations of Trimbow compared to same dose of glycopyrronium bromide and Fostair in healthy volunteers	For the glycopyrronium bromide component, the ratio of adjusted geometric mean ratios (GMR) were within the bioequivalence limits of 80 to125% for maximum plasma concentration (C_{max}) but not for area under the serum concentration time curve from time 0 to the last measurable concentration ($AUC_{0-\tau}$), the systemic exposure of glycopyrronium bromide was approximately 1.13 fold higher. For both the formoterol and beclometasone-17-monopropionate (B17MP) components in plasma, the 90% confidence intervals (CI) for the GMRs were within the bioequivalence limits for C_{max} and $AUC_{0-\tau}$.
Glyco 1	Healthy volunteers	For glycopyrronium bromide, the bioavailability of inhaled versus intravenous (IV) delivery is around 12%. Bioavailability with and without charcoal was similar, indicating minimal oral absorption.
Triple 4	Single dose clinical pharmacology in COPD patients after 4 inhalations of Trimbow using the standard actuator with or without AeroChamber Plus Flow-Vu VHC space	C_{max} was increased by 58%, while, $AUC_{0-\tau}$ was reduced by 24% after inhalation with spacer compared to without a spacer. B17MP C_{max} was increased by 15%, while $AUC_{0-\tau}$ was reduced by 37% after inhalation with spacer compared to without a spacer. Glycopyrronium bromide $AUC_{0-\tau}$ and C_{max} were higher by approximately 60% and 45% after

Study name	Description	Findings
		inhalation of Trimbow with spacer compared to inhalation without spacer
Glyco 2	Investigated the bronchodilator efficacy and safety after single and repeated administrations of different doses (12.5 µg, 25 µg, 50 µg, 100 µg and 200 µg) of glycopyrronium bromide pMDI in patients with moderate to severe COPD.	Following a single dose of glycopyrronium bromide, large positive changes from Baseline in forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) values were observed. The highest mean FEV_1 and FVC values were observed during the first 4 hours after inhalation. After 7 days of treatment with multiple doses of glycopyrronium bromide pMDI, at 12 hours post-dose, trough FEV_1 comparison was higher with glycopyrronium bromide compared to placebo. The higher the glycopyrronium bromide dose the greater the improvement in a range of lung function derived parameters. However, no statistically significant differences were established between the 50 µg and 100 µg glycopyrronium bromide pMDI doses with respect to the derived lung function and body plethysmographic parameters. The 50 µg daily glycopyrronium bromide dose was chosen for the proposed FDC.
Triple 10	In severe renal insufficiency	Glycopyrronium bromide area under the serum concentration time curve (AUC) increased up to 3 fold in patients with severe renal insufficiency
Triple 1	Examined the interaction between glycopyrronium bromide and formoterol fumarate in healthy subjects	No significant effect
Triple 12	Examined the effect of inhibition of organic cation transport in the kidneys using steady-state cimetidine on the PKs of a single dose of glycopyrronium bromide pMDI in healthy volunteers.	The results indicated that glycopyrronium bromide C_{max} and $AUC_{0-\tau}$ were increased by 16% and 26%, respectively in the presence of cimetidine compared to when Trimbow pMDI was administered alone. Similarly, formoterol $AUC_{0-\tau}$ was increased (21%) in the presence of cimetidine, whereas, formoterol C_{max} was unaffected. For B17MP, no statistically significant difference was found between treatments in terms of B17MP C_{max} or AUC

Compared to the administration of Fostair and glycopyrronium, there was a small difference in glycopyrronium bromide $AUC_{0-\tau}$ (1.13 fold increase) following administration of Trimbow. This is unlikely to be clinically significant. Use of a spacer increased C_{max} and alters AUC of the components. This is adequately described in the PI. The clinical significance of this is difficult to assess, particularly because patients use a spacer when they are unlikely to be able to use an inhaler well.

Efficacy

Study triple 5 (comparison to ICS/LABA)

This was a Phase III, 52 week, double blind, randomised, multinational, multicentre, 2 arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide administered via pMDI (Trimbow) versus fixed combination of beclometasone dipropionate and formoterol fumarate (Fostair) administered via pMDI in patients with COPD. The primary objective was to demonstrate the superiority of Trimbow over Fostair in terms of lung function (change from Baseline in pre-dose and 2-hour post-dose morning FEV_1 at Week 26) and dyspnoea (transition dyspnea index (TDI) focal score at Week 26). The secondary objectives were to evaluate the effects of Trimbow on other lung function parameters, patient's health status, clinical outcome measures and COPD exacerbations.

During the run in period, patients discontinued their usual treatment and commenced Fostair.

Inclusion criteria was age > 40 years, diagnosis of COPD, one COPD exacerbation in the 12 months prior to randomisation, FEV_1 < 50%, FEV_1/FVC < 0.7 after bronchodilator, COPD assessment test (CAT);[9] score ≥ 10, BDI ≤ 10, previously treated with ICS/LABA, LAMA/LABA or LAMA.

During the 52 week treatment period, the test treatment was Trimbow pMDI 2 puffs BID. The reference treatment was Fostair pMDI. The study treatments were administered using a standard actuator. If patients inhaled their usual COPD pMDI treatments with a spacer device, they were provided with the AeroChamber Plus to be used when taking the pMDI study treatments.

Statistics and sample size: 1304 patients (652 patients per group) were randomised in order to reach a total of 1088 evaluable patients at Week 26. This sample size provided approximately 97.7% power to detect a mean difference in favour of Trimbow pMDI in change from Baseline in pre-dose morning FEV_1 of 60 mL (at a two sided significance level of 0.05, assuming an standard deviation (SD) of 250 mL),) and 87.1% power to detect a mean difference of 0.6 units in TDI focal score (at a two sided significance level of 0.05, assuming an SD of 3.2 units).

Note: clinically significant difference in FEV_1 is 100 mL and TDI is 1.

Primary efficacy variables were considered statistically in hierarchical order.

1368 subjects were randomised. Overall 22.7% had very severe airflow limitation. About 5% of patients in each group had major protocol deviations due to noncompliance. Mean time since COPD diagnosis was 7.7 years. 72.6% of patients were on ICS/LABA at study entry, 14.8% LABA/LAMA, 11.1% LAMA. The patient population were highly symptomatic, CAT;[9] score 20.8 and St. George's Respiratory Questionnaire (SGRQ);[10] 51.3 at Baseline.

In the primary efficacy analysis on the intent-to-treat (ITT) population, the adjusted mean change in pre-dose morning FEV_1 from Baseline to Week 26 with Trimbow pMDI was 0.082 L; 95% CI: 0.062; 0.102,(p < 0.001), compared to no change with Fostair pMDI (0.001 L; 0.019; 0.021, p = 0.922). The difference between treatments was statistically significant in favour of Trimbow (p < 0.001).

[9] The **COPD Assessment Test (CAT)** is a questionnaire for people with COPD. It is designed to measure the impact of COPD on a person's life, and how this changes over time. The CAT is simple to administer, and aims to help clinicians, with their patients, better manage COPD.
[10] The **St. George's Respiratory Questionnaire (SGRQ)** is a disease-specific questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.

At Week 26, the other co-primary endpoint of adjusted mean change from Baseline to Week 26 in 2 hour post dose FEV_1 was 0.261 L (0.240; 0.283) with Trimbow and 0.145 L (0.123; 0.166) with Fostair ($p < 0.001$ for both treatments), representing an adjusted mean difference between treatments of 0.117 L ($p < 0.001$).

There was no statistically significant difference between treatment groups in mean TDI focal scores at Week 26 in both ITT and per protocol (PP) analyses. Subgroup analysis by severity of COPD showed greater difference for with those with severe (but not very severe) COPD.

There were less exacerbations with Trimbow than Fostair. This was seen in a number of the parameters related to exacerbations.

Study triple 6 (versus tiotropium)

This was a Phase III multicentre randomised controlled trial (RCT) of Trimbow versus tiotropium (18 µg daily) versus Fostair and tiotropium in patients with COPD. The primary objective was to demonstrate superiority of Trimbow over tiotropium in terms of moderate-severe COPD exacerbations over 52 weeks of treatment. The key secondary objectives were to demonstrate superiority of morning baseline FEV_1 and non inferiority of Trimbow versus Fostair and tiotropium in terms of pulmonary function. There were a number of other secondary endpoints related to quality of life, and PK.

The study included a pre-screening visit, 2 weeks run in period and 52 weeks treatment period. During the run in period, all patient received tiotropium handihaler OD. Patients were randomised 2:2:1 at the end of the run in phase. Patients were given the Aerochamber spacer if they usually used a spacer.

2691 patients were randomised to one of three treatment groups. The rate of discontinuation in the tiotropium group was double for the other groups. The rate of noncompliance varied from 3.3 to 5.8%. The mean time since the diagnosis of COPD was 8 years. 20% were using a spacer device. At Baseline, most were taking ICS/LABA (73.8%), LAMA/LABA (12%), LAMA (11.1%), No patients were on triple therapy at Baseline. The percentage of patients with severe or very severe COPD was around 20% in each group. The overall mean CAT;[9] score was 21.6 and mean SGRQ;[10] was 54.2%.

The number of exacerbations was lower in those randomised to Trimbow than tiotropium in terms of number of patients (32.6% versus 35.7%) and number of exacerbations (485 versus 569). The adjusted exacerbation rate was 0.801 (85%; CI: 0.693; 0.092). The adjusted mean change in pre-dose morning FEV_1 from Baseline to Week 52 was 0.082L, 0.021L and 0.085L in the Trimbow, tiotropium and Fostair plus tiotropium groups, respectively. The difference between Trimbow and tiotropium was 0.061L (95% CI: 0.037; 0.086; $p < 0.001$).

The adjusted mean change from Baseline in SGRQ;[10] total score was a statistically significant decrease (for example. improvement) with all three treatments at Week 52 (5.74, 4.14 and 7.32, respectively, $p < 0.001$ for all treatments).

Triple 3

This was a Phase II, multicentre, randomised, double-blind, active-controlled, 4 way cross-over, multiple dose study designed to evaluate the efficacy of a free combination of LAMA plus glycopyrronium bromide at three dose levels (25 µg, 50 µg or 100 µg daily) with fixed combination Fostair (beclometasone dipropionate/formoterol fumarate 400 µg/24 µg daily) versus. Fostair alone, administered by pMDI over a 7-day treatment period in patients with COPD. The main outcome criteria was FEV_1 area under the serum concentration time curve between 0 and 12 hours (AUC_{0-12}) normalised by time on Day 7. The investigational phase lasted approximately seven weeks and comprised four treatment periods (each of 7 days duration). Each patient was randomised to one of four

treatment sequences arranged in a 4 x 4 Williams design, and received all four treatments during the study. Each treatment period was separated by a wash-out period of 7 days on Fostair. Mean FEV_1 AUC_{0-12} normalised by time on Day 7 was higher with any Fostair plus glycopyrronium bromide combination than with Fostair alone.

Overall, the results of this study showed that the free combination Fostair plus glycopyrronium bromide resulted in greater benefit than Fostair alone. Although the greatest improvements in terms of pulmonary function and symptoms-based parameters were seen with Fostair plus glycopyrronium bromide 100 µg, the efficacy profile observed with the intermediate dose of glycopyrronium bromide (Fostair plus glycopyrronium bromide 50 µg) was better than the one observed with the lowest dose of glycopyrronium bromide (Fostair plus glycopyrronium bromide 25 µg) and not significantly different from Fostair plus glycopyrronium bromide 100 µg.

Study triple 9

This was a Phase IIb randomised, multinational, double blind, cross over placebo controlled study evaluating the effect of glycopyrronium bromide versus placebo in patients with moderate-severe COPD. The main outcome was pre-dose morning FEV_1 on Day 28. Key secondary outcome was FEV_1 AUC_{0-12} on Day 28. There was a screening visit then a 2 weeks run in period were patients were treated with beclometasone dipropionate at a dose equipotent to the patients previous treatment.

The change from Baseline in pre-morning FEV_1 on Day 28 was higher with glycopyrronium bromide than with placebo in the ITT population with a difference in adjusted means of 0.088 L (95% CI: 0.039 L; 0.137 L; $p < 0.001$).

Study triple 7

This was a Phase IIIb, randomised, open-label, active-controlled, multinational, multicentre, 26 week, 2 arm, parallel group study to evaluate the non-inferiority of the proposed FDC of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide (beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide) administered via pMDI versus FDC of fluticasone furoate/ vilanterol administered via dry powder inhaler (DPI) (Relvar) plus tiotropium bromide (Spiriva) for the treatment of patients with COPD. Primary objective was a non inferiority study for quality of life. There was a 2 weeks run in period where patients received tiotropium. The non-inferiority of Trimbow relative to fluticasone/vilanterol plus tiotropium was demonstrated by an upper confidence limit of the adjusted mean difference between treatments at Week 26 below 4 units. The changes pre-dose morning FEV_1 seen with fluticasone/ vilanterol plus tiotropium were greater than with Trimbow at all visits (adjusted mean differences at Weeks 4, 12 and 26: -0.040 L, -0.043 L and -0.048 L, respectively). There were similar number of nocturnal events and exacerbations in each group.

Study triple 8 (versus LAMA/LABA)

This was a Phase IIIb, 52 week, double blind, double dummy, randomised, multinational, multicentre, 2-arm parallel group, active controlled clinical trial of fixed combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide administered via pMDI versus indacaterol/ glycopyrronium (Ultibro) via DPI in patients with COPD (Tribute). The primary objective was to demonstrate the superiority of Trimbow over Ultibro in terms of moderate and severe COPD exacerbation rate over 52 weeks of treatment. 1532 patients were randomised. The percentage of patients who experienced moderate and severe COPD exacerbations and the number of COPD exacerbations were lower with Trimbow (35.7% and 433 events, respectively) than with indacaterol/glycopyrronium bromide (37.5% and 485 events, respectively). The adjusted exacerbation rate (for moderate to severe exacerbations) per patient per year was lower with Trimbow than with indacaterol/glycopyrronium bromide (0.504 versus 0.595;

relative risk (RR) = 0.848, 95% CI: 0.723, 0.995; p = 0.043). There was an increase in FEV_1 and improvement in SGRQ;[10] for Trimbow compared to Ultibro. However, these small numerical improvements in above parameters did not lead to any change in use of rescue medication, nocturnal symptoms and CAT score;[9] which were comparable between treatments.

Safety

The Phase III and IIIb studies included a large number of patients studied over 52 weeks.

The integrated safety analysis for the two pivotal studies, Studies Triple 5 and Triple 6, involved 1764 patients treated with beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide. Approximately 55% of patients had one treatment emergent adverse event (TEAE). The most common TEAEs were COPD exacerbation, nasopharyngitis, headache, pneumonia, dyspneoa, hypertension, respiratory tract infection and cough.

The number of TEAEs in Studies Triple 7 and Triple 8 was similar in the beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide groups and fluticasone/vilanterol and tiotropium groups.

An integrated analysis of treatment-emergent adverse drug reactions (ADR) with beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide pooled from all Phase III and IIIb studies (Studies Triple 5, Triple 6, Triple 7 and Triple 8) showed a low rate of 3.6% (112 patients reported 138 ADRs). The most common treatment-emergent ADRs (for example, ADRs reported in ≥ 2 patients) by decreasing order of overall frequency were: oral candidiasis; dry mouth; muscle spasms; dysphonia; hypertension; oral fungal infection; cough; stomatitis; alopecia; atrial fibrillation; electrocardiogram QT (QT interval);[11] prolonged; headache; nausea; oropharyngeal candidiasis; pruritus; throat irritation.

In the pivotal Phase III studies integrated safety analysis, the incidence of death was low and similar across the 4 treatment groups (around 2%). The most common TEAEs leading to death were cardiac disorders with slightly higher incidence in the tiotropium group (0.7%, 1.0%, 1.3% and 0.4%, respectively). The incidence of deaths due to COPD exacerbations was around 0.4%. The most common serious adverse event (SAE) by preferred term (for example, SAEs reported in > 3 patients with any treatment) in decreasing order of overall frequency were: COPD exacerbation; pneumonia; cardiac failure; myocardial ischaemia; ischaemic stroke; atrial fibrillation; lung neoplasm malignant; coronary artery disease; respiratory failure; cardiac failure acute. COPD exacerbations were more common in the beclometasone dipropionate/formoterol fumarate group.

In the Phase III pivotal studies, an independent Adjudication Committee (AC) was established to assess potentially relevant adverse events (AEs) as part of the Major Adverse Cardiovascular Event (MACE) evaluation. The percentage of patients reported with a treatment-emergent MACE was slightly lower with beclometasone dipropionate/formoterol fumarate plus tiotropium (1.3%) than with the other three treatments (ranging from 2.0% to 2.2%). There were small changes in heart rate in Studies Triple 5, 6 and 7, which were of unknown significance.

[11] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

In the integrated safety analysis, there was a trend toward a slightly higher rate of pneumonia in the groups receiving glycopyrronium bromide than other groups.

CARSAF trial (primarily safety study)

This was a Phase II, randomised, double blind, active controlled, 3 arm parallel group, multi-national, multi-centre study to evaluate the cardiac safety of two doses of glycopyrronium bromide (25 µg and 50 µg BID) both combined with Fostair 100/6 µg BID versus Foster 100/6 µg BID alone in patients with moderate to severe COPD. 191 patients were randomised. Eligible patients included male or female patients aged ≥ 40 years with a diagnosis of severe or very severe COPD made at least 12 months prior to screening (according to GOLD;[2] guidelines, updated 2014). The primary endpoint of the CARSAF trial was the change from Baseline in average 24-hour heart rate at Visit 5. The change from Baseline in average 24-hour heart rate at Day 14 was analysed using an analysis of covariance (ANCOVA) model including treatment and country as factors and Baseline average 24 hour heart rate as a covariate. There were a number of secondary endpoints.

Results showed that 14 day treatment with Fostair (beclometasone dipropionate/ formoterol fumarate 100/6 µg BID) given in combination with glycopyrronium bromide 12.5 µg or 25 µg BID was not associated with an increased risk of elevation of heart rate (measured by means of 24-hour digital ECG Holter);[12] in comparison with Fostair given alone. However the upper 97.5% CI bound slightly exceeded (0.226 beats per minute in 24 hours) the pre-defined margin of equivalence in the comparison between Fostair combined with glycopyrronium bromide 50 µg/day and Fostair given alone. Equivalence in the primary study endpoint between Fostair combined with glycopyrronium bromide 100 µg/day and Fostair given alone was fully demonstrated. None of patients in any group had clinically significant prolongation of the Fridericia-corrected QT interval (QTcF);[13] interval. There were no substantial differences between groups in incidence of 24 hour digital ECG Holter abnormal findings.

Among the reported ADRs, the following are usually associated with:

- Beclometasone dipropionate: pneumonia, oral fungal infections, lower respiratory tract infection fungal, dysphonia, throat irritation, hyperglycaemia, psychiatric disorders, cortisol decreased, blurred vision.
- Formoterol fumarate: hypokalaemia, hyperglycaemia, tremor, palpitations, muscle spasms, ECG – QT;[11] prolonged, blood pressure increased and decreased, atrial fibrillation, tachycardia, tachyarrhythmia, angina pectoris (stable and unstable), ventricular extrasystoles, nodal rhythm.
- Glycopyrronium bromide: glaucoma, atrial fibrillation, tachycardia, palpitations, dry mouth, dental caries, dysuria, urinary retention, urinary tract infection.

Overall, safety results with proposed triple FDC of beclometasone dipropionate, formoterol fumarate/glycopyrronium bromide were consistent with known AEs associated with individual ingredients of the FDC.

[12] An ECG holter is a small digital device that records the rhythm of the heart over a period of time; this rhythm is also known as the heart's electrical activity. The Holter monitor is an ambulatory, portable ECG machine that helps to provide particular information about the heart. It is worn over a period of 24 hours.
[13] QTcF is a formula which takes into account the account the physiologic shortening of the QT interval which occurs as the heart rate increases, permitting comparison of the QT interval across a range of rates. It theoretically corrects the QT interval to that which would be observed at a heart rate of 1 cycle per second.

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[14]

The sponsor submitted European Union (EU) risk management plan (RMP) version 6 and Australia-Specific Annex (ASA) version 1.0.

The summary of safety concerns included the following:

- Identified risks: none
- Potential risks: heart disease and stroke
- Missing information: none
- Routine pharmacovigilance and risk mitigation is proposed.

Risk-benefit analysis

Delegate's considerations

The dossier is based upon providing evidence of the additional benefits of glycopyrronium (LAMA) in addition to previously approved Fostair pMDI (beclometasone and formoterol) in the management of COPD. The device used is the same as that used for Fostair.

The clinical trials submitted were in patients with moderate to severe COPD. The pivotal studies showed that Trimbow was superior to Fostair (beclometasone dipropionate and formoterol fumarate) for FEV_1 symptoms, COPD exacerbations and quality of life. Trimbow was superior to tiotropium for exacerbations, lung function, symptoms and quality of life. There was some benefit in exacerbations and lung function compared to indacterol and glycopyrronium, however the significant improvement in lung function in the run in period of this study may have minimised any potential benefits to be identified. Trimbow was non inferior to combined treatment with Fostair and tiotropium for quality of life measure. Trimbow also showed similar efficacy to a combination of Fostair and tiotropium.

The safety profile was consistent with the known safety profile for this combination therapy.

The treatment algorithm for COPD depends upon symptoms and severity. Treatment generally commences with a bronchodilator (LAMA or LABA), the next step up may then be another bronchodilator or if the patient is having frequent exacerbations an ICS. Triple therapy is generally used only for those with severe disease, for example low FEV_1 and frequent exacerbations. The patient population in the dossier included those with moderate to severe and very severe disease. Although some of these patients were just on a single bronchodilator and may have reasonable control on dual therapy, overall the patient population was appropriate for the purpose of the application.

The combined treatment with ICS/LAMA/LABA is recognised in the management of COPD, although there may be some difference in efficacy and safety of the different medications within each of these broad classes. Combining these treatments in a single inhaler has benefits over the use of two of three separate inhalers.

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

Proposed action

The Delegate had no clinical concerns about the registration of this product. The final approval is subjected to the recommended amendments to the PI.

Advisory Committee considerations[15]

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, TGA approved the registration of Trimbow (100 µg beclometasone dipropionate, 6 µg formoterol fumarate dihydrate and 12.5 µg glycopyrronium bromide (glycopyrrolate,)) pressurised inhalation solution, indicated for:

> *Trimbow is indicated for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting beta2-agonist (LABA) or a combination of a LABA and a long-acting muscarinic antagonist (LAMA)*

Specific conditions of registration applying to these goods

This approval does not impose any requirement for the submission of periodic safety update reports (PSURs). It is 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 Trimbow 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>.

[15] 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.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au