AUSTRALIAN PRODUCT INFORMATION - TRIMBOW® (beclometasone dipropionate, formoterol (eformoterol) fumarate dihydrate and glycopyrronium bromide (glycopyrrolate) pressurised inhalation solution

1. NAME OF THE MEDICINE

Beclometasone dipropionate, formoterol (eformoterol) fumarate dihydrate and glycopyrronium bromide (glycopyrrolate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose (the dose leaving the valve) contains 100 micrograms of beclometasone dipropionate (BDP), 6 micrograms of formoterol fumarate dihydrate (FF) and 10 micrograms of glycopyrronium (equivalent to 12.5 micrograms of glycopyrronium bromide) (GB).

Each delivered dose (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (equivalent to 11 micrograms of glycopyrronium bromide) (GB).

List of excipient(s) with known effect: alcohol.

For the full list of excipients see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Pressurised inhalation solution (pressurised inhalation).
Colourless to yellowish liquid solution.

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve. The canister is inserted into a polypropylene plastic actuator which incorporates a mouthpiece and is fitted with a plastic protective cap. The actuator is grey with a red cap. The actuator has a dose counter.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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)

4.2 DOSE AND METHOD OF ADMINISTRATION

TRIMBOW is for inhalation use.

DOSAGE

TRIMBOW is not to be used as initial therapy but may be considered as step-up from LABA/LAMA or ICS/LABA or for patients already taking ICS+LABA+LAMA. Patients can be changed from their existing inhalers to TRIMBOW at the next dose. It is important, however, that patients do not take other LABA, LAMA or ICS while taking TRIMBOW.

A stepwise approach to the management of COPD is recommended, including the cessation of smoking and a pulmonary rehabilitation program.

Adults

The recommended dose is two inhalations of TRIMBOW 100/6/12.5 twice daily. The patient should take two inhalations in the morning and two inhalations in the evening at the same time every day.

The maximum dose is two inhalations of TRIMBOW twice daily.

Special populations

Paediatric population

There is no relevant use of TRIMBOW in the paediatric population (under 18 years of age) for the indication of COPD.

Elderly

No dosage adjustment is required in elderly patients (65 years of age and older) (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Renal impairment

TRIMBOW can be used at the recommended dose in patients with mild to moderate renal impairment. Use of TRIMBOW in patients with severe renal impairment or end-stage renal disease requiring dialysis, especially if associated with significant body weight reduction, should be considered only if the expected benefit outweighs the potential risk (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Hepatic impairment

There are no relevant data on the use of TRIMBOW in patients with severe hepatic impairment and the medicinal product should be used with caution in these patients (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

METHOD OF ADMINISTRATION

TRIMBOW is for oral inhalation only. After inhaling, patients should rinse their mouth or gargle with water without swallowing it or brush their teeth (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler correctly by a physician or other healthcare professional, who should also

regularly check the adequacy of the patient's inhalation technique. The patient should be advised to read the Package Leaflet carefully and follow the instructions for use as given in the leaflet.

TRIMBOW is provided with a dose counter or dose indicator on the back of the inhaler, which shows how many actuations are left. For the 120 actuation pressurised container each time the patient presses the container a puff of the solution is released and the counter counts down by one.

Patients should be advised not to drop the inhaler as this may cause the counter to count down.

Priming the inhaler

Before using the inhaler for the first time, the patient should release one actuation into the air in order to ensure that the inhaler is working properly (priming). Before priming the 120 actuation pressurised containers, the counter/indicator should read 121. After priming, the counter/indicator should read 120.

Use of the inhaler

Patients should stand or sit in an upright position when inhaling from their inhaler. The steps below should be followed. IMPORTANT: steps 2 to 5 should not be performed too quickly:

1. Patients should remove the protective cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt or any other foreign objects.
2. Patients should breathe out slowly and as deeply as comfortable, in order to empty their lungs.
3. Patients should hold the inhaler vertically with its body upwards and place the mouthpiece between their teeth without biting. Their lips should then be placed around the mouthpiece, with the tongue flat under it.
4. At the same time, patients should breathe in slowly and deeply through the mouth until the lungs are full of air (this should take approximately 4 – 5 seconds). Immediately after starting to breathe in, patients should firmly press down on the top of the pressurised container to release one puff.
5. Patients should then hold their breath for as long as comfortably possible, then remove the inhaler from the mouth and breathe out slowly. Patients should not breathe out into the inhaler.
6. Patients should then check the dose counter or dose indicator to ensure it has moved accordingly.

To inhale the second puff, patients should keep the inhaler in a vertical position for approximately 30 seconds and repeat steps 2 to 6.

If mist appears after the inhalation, either from the inhaler or from the sides of the mouth, the procedure should be repeated from step 2.

After use, patients should close the inhaler with the protective mouthpiece cover and check the dose counter or dose indicator.

After inhaling, patients should rinse their mouth or gargle with water without swallowing it or brush their teeth (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

When to get a new inhaler
Patients should be advised to get a new inhaler when the dose counter or indicator shows the number 20. They should stop using the inhaler when the counter or indicator shows 0 as any puffs left in the device may not be enough to release a full actuation.

Additional instructions for specific groups of patients
For patients with weak hands it may be easier to hold the inhaler with both hands. Therefore, the index fingers should be placed on the top of the pressurised container and both thumbs on the base of the inhaler.

Patients who find it difficult to synchronise aerosol actuation with inspiration of breath may use the AeroChamber Plus spacer device, properly cleaned as described in the relevant leaflet. They should be advised by their doctor or pharmacist about the proper use and care of their inhaler and spacer and their technique checked to ensure optimum delivery of the inhaled active substance to the lungs. This may be obtained by the patients using the AeroChamber Plus by one continuous slow and deep breath through the spacer, without any delay between actuation and inhalation. Alternatively, patients may simply breathe in and out (through the mouth) after the actuation, as instructed in the spacer leaflet, to obtain the active substance. See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 5.2 PHARMACOKINETIC PROPERTIES.

Cleaning
For the regular cleaning of the inhaler, patients should remove weekly the cap from the mouthpiece and wipe the outside and inside of the mouthpiece with a dry cloth. They should not remove the pressurised container from the actuator and should not use water or other liquids to clean the mouthpiece.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Not for acute use
TRIMBOW is not indicated for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy).

Hypersensitivity
Immediate hypersensitivity reactions have been reported after administration of TRIMBOW. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips and face), urticaria or skin rash, TRIMBOW should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator (reliever). TRIMBOW should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary.

Deterioration of disease

It is recommended that treatment with TRIMBOW should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment, but medical attention must be sought. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of COPD is potentially life-threatening and the patient should undergo urgent medical assessment.

Cardiovascular effects

TRIMBOW should be used with caution in patients with cardiac arrhythmias, especially third-degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heart beat), idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, severe heart disease (particularly acute myocardial infarction, ischaemic heart disease, congestive heart failure), occlusive vascular diseases (particularly arteriosclerosis), arterial hypertension and aneurysm.

Caution should also be exercised when treating patients with known or suspected prolongation of the QTc interval (QTc > 450 milliseconds for males, or > 470 milliseconds for females), either congenital or induced by medicinal products as these patients were excluded from clinical trials with TRIMBOW.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that TRIMBOW is not administered for at least 12 hours before the start of anaesthesia as there is a risk of cardiac arrhythmias.

Caution is also required when TRIMBOW is used by patients with thyrotoxicosis, diabetes mellitus, pheochromocytoma and untreated hypokalaemia.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose, but this has not been demonstrated conclusively. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD. These factors should be considered when TRIMBOW is prescribed, and treatment re-evaluated if pneumonia occurs.

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. The daily dose of TRIMBOW corresponds to a medium dose of inhaled corticosteroid; furthermore, these effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include: Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation, decrease in bone mineral density, cataract, glaucoma and, more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Therefore, it is important that the patient is reviewed regularly.

TRIMBOW should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Anticholinergic effect

Glycopyrronium should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or urinary retention. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using TRIMBOW and to contact their doctor immediately should any of these signs or symptoms develop.

Additionally, due to the anticholinergic effect of glycopyrronium, the long-term co-administration of TRIMBOW with other anticholinergic-containing medicinal products is not recommended (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use with a spacer

Single dose pharmacokinetic data (see section 5.2 PHARMACOKINETIC PROPERTIES) have demonstrated that in comparison with routine use without a spacer device, the use of TRIMBOW with the AeroChamber Plus spacer device increased lung availability of beclometasone 17-monopropionate (BDP main active metabolite), by 15% for C_{max} and 21% for $AUC_{0\text{-}30min}$), formoterol by 58% for C_{max} and 53% for $AUC_{0\text{-}30min}$ and glycopyrronium by 60% for both C_{max} and $AUC_{0\text{-}30min}$. The total exposure ($AUC_{0\text{-}t}$) was increased by 45% for glycopyrronium while it was decreased for beclometasone 17 monopropionate and formoterol by 37% and 24%, respectively. The observed changes are not expected to have a negative impact on efficacy since the AeroChamber Plus spacer increases the lung deposition of TRIMBOW active components. In terms of safety, available data from long-term clinical studies where the use of the AeroChamber Plus spacer was permitted have not raised any significant safety concerns (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Prevention of oropharyngeal infections

In order to reduce the risk of oropharyngeal candida infection, patients should be advised to rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling the prescribed dose.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Use in hepatic impairment

In patients with severe hepatic impairment, TRIMBOW should be used only if the expected benefit outweighs the potential risk (see section 5.2 PHARMACOKINETIC PROPERTIES). These patients should be monitored for potential adverse reactions.

Use in renal impairment

In patients with severe renal impairment, including those with end-stage renal disease requiring dialysis, especially if associated with a significant body weight reduction, TRIMBOW should be used only if the expected benefit outweighs the potential risk (see section 5.2 PHARMACOKINETIC PROPERTIES). These patients should be monitored for potential adverse reactions.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

Interactions with laboratory tests have not been established.

Hypokalaemia

Potentially serious hypokalaemia may result from beta2-agonist therapy. This has the potential to produce adverse cardiovascular effects. Particular caution is advised in severe COPD as this effect may be potentiated by hypoxia. Hypokalaemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalaemia, such as xanthine derivatives, steroids and diuretics (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Caution is also recommended when a number of reliever bronchodilators are used. It is recommended that serum potassium levels are monitored in such situations.

Hyperglycaemia

The inhalation of formoterol may cause a rise in blood glucose levels. Therefore, blood glucose should be monitored during treatment following established guidelines in patients with diabetes.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interactions

Since glycopyrronium is eliminated mainly by the renal route, drug interaction could potentially occur with medicinal products affecting renal excretion mechanisms (see section 5.2 PHARMACOKINETIC PROPERTIES). The effect of organic cation transport inhibition (using cimetidine as a probe inhibitor of OCT2 and MATE1 transporters) in the kidneys on inhaled glycopyrronium disposition showed a limited increase in its total systemic exposure (AUC_{0-t}) by 16% and a slight decrease in renal clearance by 20% due to co administration of cimetidine.

The total formoterol exposure (AUC_{0-t}) increased by 21% after co administration of TRIMBOW with cimetidine. This increased exposure was possibly related to inhibition of cytochrome P450 isozymes involved in formoterol metabolism, due to cimetidine co-administration.

Beclometasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however, the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such medicinal products.

Pharmacodynamic interactions

Related to formoterol

Non-cardioselective beta-blockers (including eye drops) should be avoided in patients taking inhaled formoterol. If they are administered for compelling reasons, the effect of formoterol will be reduced or abolished.

Concomitant use of other beta-adrenergic medicinal products can have potentially additive effects; therefore, caution is required when other beta-adrenergic medicinal products are prescribed concomitantly with formoterol.

Concomitant treatment with quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants and phenothiazines can prolong the QT interval and increase the risk of ventricular arrhythmias. In addition, L dopa, L thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors, including medicinal products with similar properties such as furazolidone and procarbazine, may precipitate hypertensive reactions.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of beta2-agonists (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Related to glycopyrronium
The long-term co-administration of TRIMBOW with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Excipients
TRIMBOW contains a small amount of ethanol absolute. There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No specific studies on fertility have been performed with TRIMBOW in humans. Impairment of fertility and inhibition of ovulation were observed in rats treated with beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide in combination (100/6/25 ratio) at oral doses ≥2 mg/kg/day. This is attributable to the beclometasone dipropionate component, and occurred only at corticosteroid exposure levels (plasma AUC) far in excess of that in patients receiving TRIMBOW. Accordingly, impairment of fertility is not expected in patients.

Use in pregnancy (Category B3)
There are no or limited amount of data from the use of TRIMBOW in pregnant women.

Studies in rats with beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide in combination (100/6/25 ratio; given orally) showed embryofetal and pup loss, dystocia, decreased fetal/pup weight, increased fetal visceral variations and impaired fetal ossification. 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 beta2-agonist, with effects observed in animals at formoterol exposure levels lower than in patients. Therefore, as a precautionary measure, it is preferable to avoid the use of TRIMBOW during pregnancy and during labour.

TRIMBOW should only be used during pregnancy if the expected benefit to the patient outweighs the potential risk to the fetus. Infants and neonates born to mothers receiving substantial doses of TRIMBOW should be observed for adrenal suppression.

Use in lactation
There are no relevant clinical data on the use of TRIMBOW during breast-feeding in humans.

Glucocorticoids are excreted in human milk. It is reasonable to assume that beclometasone dipropionate and its metabolites are also excreted into breast-milk.
It is unknown whether formoterol or glycopyrronium (including their metabolites) pass into human breast-milk but they have been detected in the milk of lactating animals. Anticholinergic agents like glycopyrronium could suppress lactation.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from TRIMBOW therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TRIMBOW has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The most frequently reported adverse events in the two Phase III, 52 week active-controlled studies in COPD (TRILOGY and TRINITY) are presented in Table 1 and Table 2.

Study TRILOGY included 687 patients with COPD who received TRIMBOW pMDI 100/6/12.5 micrograms two inhalations twice daily for up to 52 weeks, which were compared to 680 patients with COPD treated with an active comparator, a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms pMDI two inhalations twice daily.

Study TRINITY included 1077 patients with COPD who received TRIMBOW pMDI 100/6/12.5 micrograms two inhalations twice daily for up to 52 weeks, which were compared to 1076 patients with COPD treated with tiotropium bromide 18 micrograms inhalation powder, hard capsule, once daily and 537 patients with COPD treated with a two-inhaler triple therapy consisting of a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms pMDI two inhalations twice daily plus tiotropium bromide 18 micrograms inhalation powder, hard capsule, once daily.

Table 1: Adverse events with ≥1% incidence with TRIMBOW in TRILOGY clinical trial (CCD-1207-PR-0091)

	BDP/FF/GB 400/24/50 mcg[#] N=687	**BDP/FF 400/24 mcg[#] N=680**
System Organ Class, Preferred Term	**Number of patients (%)**	**Number of patients (%)**
Infections and infestations		
Nasopharyngitis	39 (5.7%)	38 (5.6%)
Pneumonia*	23 (3.3%)	18 (2.6%)
Respiratory tract infection viral	16 (2.3%)	10 (1.5%)
Oral candidiasis	13 (1.9%)	2 (0.3%)
Influenza	9 (1.3%)	5 (0.7%)
Bronchitis	9 (1.3%)	4 (0.6%)

	BDP/FF/GB 400/24/50 mcg[#] N=687	**BDP/FF 400/24 mcg[#] N=680**
System Organ Class, Preferred Term	**Number of patients (%)**	**Number of patients (%)**
Metabolism and nutrition disorders		
Diabetes mellitus	7 (1.0%)	2 (0.3%)
Nervous system disorders		
Headache	12 (1.7%)	16 (2.4%)
Cardiac disorders		
Atrial fibrillation	10 (1.5%)	9 (1.3%)
Cardiac failure	7 (1.0%)	5 (0.7%)
Vascular disorders		
Hypertension	20 (2.9%)	16 (2.4%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	214 (31.1%)	240 (35.3%)
Dyspnoea	12 (1.7%)	13 (1.9%)
Musculoskeletal and connective tissue disorders		
Muscle spasms	8 (1.2%)	4 (0.6%)

BDP/FF/GB = beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide (TRIMBOW)
BDP/FF = beclometasone dipropionate/formoterol fumarate
[#]Total daily dose
*Includes preferred terms of bronchopneumonia, pneumonia and pneumonia aspiration

Table 2: Adverse events with ≥1% incidence with TRIMBOW in TRINITY clinical trial (CCD-1208-PR-0090)

	BDP/FF/GB 400/24/50 mcg[#] N=1077	**Tiotropium 18 mcg[#] N=1076**	**BDP/FF 400/24 µg + Tiotropium 18 mcg[#] N=537**
System Organ Class, Preferred Term	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**
Infections and infestations			
Nasopharyngitis	57 (5.3%)	66 (6.1%)	20 (3.7%)
Pneumonia*	28 (2.6%)	19 (1.8%)	12 (2.2%)
Respiratory tract infection viral	15 (1.4%)	15 (1.4%)	13 (2.4%)
Influenza	15 (1.4%)	10 (0.9%)	4 (0.7%)
Viral upper respiratory tract infection	11 (1.0%)	6 (0.6%)	6 (1.1%)
Nervous system disorders			
Headache	43 (4.0%)	41 (3.8%)	18 (3.4%)
Cardiac disorders			
Atrial fibrillation	15 (1.4%)	13 (1.2%)	4 (0.7%)
Vascular disorders			

	BDP/FF/GB 400/24/50 mcg[#] N=1077	**Tiotropium 18 mcg[#] N=1076**	**BDP/FF 400/24 µg + Tiotropium 18 mcg[#] N=537**
System Organ Class, Preferred Term	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**
Hypertension	20 (1.9%)	20 (1.9%)	10 (1.9%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	351 (32.6%)	383 (35.6%)	167 (31.1%)
Dyspnoea	23 (2.1%)	37 (3.4%)	8 (1.5%)
Cough	18 (1.7%)	23 (2.1%)	9 (1.7%)
Musculoskeletal and connective tissue disorders			
Back pain	18 (1.7%)	6 (0.6%)	2 (0.4%)
General disorders and administration site conditions			
Asthenia	12 (1.1%)	7 (0.7%)	4 (0.7%)

BDP/FF/GB = beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide (TRIMBOW)
BDP/FF = beclometasone dipropionate/formoterol fumarate
[#]Total daily dose
*Includes preferred terms of bronchopneumonia, interstitial lung disease, lobar pneumonia and pneumonia

In the clinical development programme of TRIMBOW in COPD, the most frequently reported adverse reactions with TRIMBOW were oral candidiasis (which occurred in 0.8% of the exposed subjects), which is normally associated with ICS; muscle spasms (0.4%), which can be attributed to the LABA component; dry mouth (0.4%), which is a typical anticholinergic effect, which can be attributed to the LAMA component.

The clinical development programme of TRIMBOW was conducted in patients with moderate, severe or very severe COPD. A total of 3,346 patients were treated at the target dose regimen (two inhalations twice daily) in multiple dose studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 3: Adverse reactions with TRIMBOW*

MedDRA system organ class	Adverse reaction	Frequency
Infections and Infestations	Pneumonia (in COPD patients), pharyngitis, oral candidiasis, urinary tract infection[1], nasopharyngitis[1]	Common
	Influenza[1], oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis[1], sinusitis[1], rhinitis[1], gastroenteritis[1], vulvovaginal candidiasis[1]	Uncommon
	Lower respiratory tract infection (fungal)	Rare
Blood and lymphatic system disorders	Granulocytopenia[1]	Uncommon
	Thrombocytopenia[1]	Very rare
Immune system disorders	Dermatitis allergic[1]	Uncommon
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Rare
Endocrine disorders	Adrenal suppression[1]	Very rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
	Decreased appetite	Rare
Psychiatric disorders	Restlessness[1]	Uncommon
	Psychomotor hyperactivity[1], sleep disorders[1], anxiety, depression[1], aggression[1], behavioural changes (predominantly in children) [1]	Frequency not known
	Insomnia	Rare
Nervous system disorders	Headache	Common
	Tremor, dizziness, dysgeusia[1], hypoaesthesia[1]	Uncommon
	Hypersomnia	Rare
Eye disorders	Vision, blurred[1] (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Frequency not known
	Glaucoma[1], cataract[1]	Very rare
Ear and labyrinth disorders	Otosalpingitis[1]	Uncommon
Cardiac disorders	Atrial fibrillation, electrocardiogram QT prolonged, tachycardia, tachyarrhythmia[1], palpitations	Uncommon
	Angina pectoris (stable[1] and unstable), ventricular extrasystoles[1], nodal rhythm, sinus bradycardia	Rare
Vascular disorders	Hyperaemia[1], flushing[1], hypertension	Uncommon
	Extravasation blood	Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia	Common
	Cough, productive cough[1], throat irritation, epistaxis[1]	Uncommon
	Bronchospasm paradoxical[1], oropharyngeal pain, pharyngeal erythema, pharyngeal inflammation, dry throat	Rare
	Dyspnoea[1]	Very rare
Gastrointestinal disorders	Diarrhoea[1], dry mouth, dysphagia[1], nausea, dyspepsia[1], burning sensation of the lips[1], dental caries[1], (aphthous) stomatitis	Uncommon
Skin and subcutaneous tissue disorders	Rash[1], urticaria[1], pruritus, hyperhidrosis[1]	Uncommon
	Angioedema[1]	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia, pain in extremity[1], musculoskeletal chest pain[1]	Uncommon
	Growth retardation[1]	Very rare
Renal and urinary disorders	Dysuria, urinary retention, nephritis[1]	Rare

MedDRA system organ class	Adverse reaction	Frequency
General disorders and administration site conditions	Fatigue[1]	Uncommon
	Asthenia	Rare
	Oedema peripheral[1]	Very rare
Investigations	C-reactive protein increased[1], platelet count increased[1], free fatty acids increased[1], blood insulin increased[1], blood ketone body increased[1], cortisol decreased[1]	Uncommon
	Blood pressure increased[1], blood pressure decreased[1]	Rare
	Bone density decreased[1]	Very rare

*****Includes adverse drug reactions reported in the clinical development of TRIMBOW and adverse drug reactions reported for the marketed individual components BDP/FF and GB

[1]Adverse reactions reported in the SmPC of at least one of the individual components, but not observed as adverse reactions in the clinical development of TRIMBOW.

Among the observed adverse reactions, the following are typically associated with:

Beclometasone dipropionate: pneumonia, oral fungal infections, lower respiratory tract infection fungal, dysphonia, throat irritation, hyperglycaemia, psychiatric disorders, cortisol decreased, blurred vision.

Formoterol: hypokalaemia, hyperglycaemia, tremor, palpitations, muscle spasms, electrocardiogram QT prolonged, blood pressure increased, blood pressure decreased, atrial fibrillation, tachycardia, tachyarrhythmia, angina pectoris (stable and unstable), ventricular extrasystoles, nodal rhythm.

Glycopyrronium: glaucoma, atrial fibrillation, tachycardia, palpitations, dry mouth, dental caries, dysuria, urinary retention, urinary tract infection.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

An overdose of TRIMBOW may produce signs and symptoms due to the individual component's actions, including those seen with overdose of other beta2-agonists or anticholinergics and consistent with the known inhaled corticosteroid class effects (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If overdose occurs, the patient's symptoms should be treated supportively with appropriate monitoring as necessary.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids.
ATC code: R03AL09.

MECHANISM OF ACTION

TRIMBOW contains beclometasone dipropionate, formoterol and glycopyrronium in a solution formulation resulting in an aerosol with extrafine particles with an average mass median aerodynamic diameter (MMAD) of around 1.1 micrometres and co-deposition of the three components. The aerosol particles of TRIMBOW are on average much smaller than the particles delivered in non-extrafine formulations. For beclometasone dipropionate, this results in a more potent effect than formulations with a non-extrafine particle size distribution (100 micrograms of beclometasone dipropionate extrafine in TRIMBOW are equivalent to 250 micrograms of beclometasone dipropionate in a non-extrafine formulation).

Beclometasone dipropionate

Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs. Glucocorticoids are widely used for the suppression of inflammation in chronic inflammatory diseases of the airways such as COPD. Their action is mediated by the binding to glucocorticoid receptors in the cytoplasm resulting in the increased transcription of genes coding for anti-inflammatory proteins.

Formoterol

Formoterol is a selective beta2 adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

Glycopyrronium

Glycopyrronium is a high-affinity, long-acting muscarinic receptor antagonist (anticholinergic) used for inhalation as bronchodilator treatment of COPD. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways. It shows greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor.

CLINICAL TRIALS

All patients included in the below described clinical studies were required to have a clinical diagnosis of COPD, a smoking history of at least 10 pack years; a post-salbutamol FEV_1/ FVC ratio <0.70 and FEV_1 of <50% predicted normal; evidence of symptoms with a COPD Assessment Test (CAT) score of 10 or above; and a history of ≥1 COPD exacerbation in the previous 12 months at screening.

Study 1 (CCD-1207-PR-0091, TRILOGY)

The efficacy of the single-inhaler fixed triple combination of beclomethasone dipropionate, formoterol fumarate, glycopyrronium bromide (BDP/FF/GB 100/6/12.5 micrograms) pMDI administered as a two inhalations twice-daily treatment in patients with a clinical diagnosis of COPD has been evaluated in this multicentre, randomised double-blind, parallel group 52-week active-controlled study compared to the fixed combination pMDI - beclomethasone dipropionate, formoterol fumarate (BDP/FF 100/6 micrograms) two inhalations twice-daily.

At screening, the mean post-bronchodilator FEV_1 was 36.5% predicted, the mean reversibility was 10.40%, and the mean CAT score was 20.8. In the year prior to study entry, 80.2% of the patients had one moderate or severe COPD exacerbation, while 19.8% of the patients had experienced more than one exacerbation.

BDP/FF/GB demonstrated a statistically significant improvement in lung function (as defined by change from baseline in pre-dose FEV_1 at Week 26 and change from baseline in 2-hour post-dose FEV_1; co-primary endpoints) compared with BDP/FF (see Table 4).

BDP/FF/GB showed a numerical improvement compared with BDP/FF at Week 26 for dyspnea severity measured by the transition dyspnea index (TDI) focal score (co-primary endpoint) and health-related quality of life measured by the St. George's Respiratory Questionnaire (SGRQ) total score. BDP/FF/GB also demonstrated a reduction in the annual rate of moderate/severe exacerbations (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation) compared with BDP/FF (see Table 4).

The lung function, TDI and SGRQ outcomes at Week 52 (data not shown) were consistent with the results observed at Week 26 (see Table 4).

Table 4: Key efficacy endpoints, ITT population (Study CCD-1207-PR-0091, TRILOGY)	BDP/FF/GB 100/6/12.5 mcg (n = 687)	BDP/FF 100/6 mcg (n = 680)
Primary endpoints		
Change from baseline in pre-dose morning FEV_1 (L) at Week 26 (L)		
n Adjusted mean (95% CI)	642 0.082 (0.062; 0.102)	616 0.001 (-0.019; 0.021)
Adjusted mean difference (95% CI) p-value	0.081 (0.052; 0.109) < 0.001	
Change from baseline in 2-hour post-dose FEV_1 (L) at Week 26 (L)		
n Adjusted mean (95% CI)	631 0.261 (0.240; 0.283)	609 0.145 (0.123; 0.166)
Adjusted mean difference (95% CI) p-value	0.117 (0.086; 0.147) < 0.001	
TDI focal score at Week 26		
n Adjusted mean (95% CI)	642 1.71 (1.50; 1.92)	609 1.50 (1.29; 1.71)
Adjusted mean difference (95% CI) p-value	0.21 (-0.08; 0.51) 0.160	
Secondary endpoints		

Change from baseline in pre-dose morning FEV_1 (L) at Week 52 (L)		
n Adjusted mean (95% CI)	606 0.071 (0.050; 0.093)	578 0.008 (-0.014; 0.030)
Adjusted mean difference (95% CI)	0.063 (0.032; 0.094)	
Change from baseline in 2-hour post-dose FEV_1 (L) at Week 52 (L)		
n Adjusted mean (95% CI)	598 0.249 (0.226; 0.273)	575 0.146 (0.122; 0.170)
Adjusted mean difference (95% CI)	0.103 (0.069; 0.137)	
TDI focal score at Week 52		
n Adjusted mean (95% CI)	608 2.03 (1.81; 2.25)	579 1.81 (1.59; 2.04)
Adjusted mean difference (95% CI)	0.21 (-0.10; 0.53)	
Moderate/severe COPD exacerbation rate		
Adjusted exacerbation rate per patient per year (95% CI)	0.410 (0.358; 0.469)	0.530 (0.468; 0.600)
Adjusted rate ratio (95% CI)	0.773 (0.647; 0.924)	

BDP= beclomethasone dipropionate; CAT= COPD assessment test; COPD= chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; FF= formoterol fumarate; GB= glycopyrronium bromide; n= number of patients with available data; N= Number of patients in the ITT population; TDI= transitional dyspnoea index.

Study 2 (CCD-1208-PR-0090, TRINITY)

The efficacy of the single-inhaler fixed triple combination of beclomethasone dipropionate, formoterol fumarate, glycopyrronium bromide (BDP/FF/GB 100/6/12.5 micrograms) pMDI administered as two inhalations, twice-daily treatment in patients with a clinical diagnosis of COPD has been evaluated in this multicentre, double-blind, double-dummy, parallel group 52-week active-controlled study. It was compared to tiotropium bromide (TIO 18 micrograms) inhalation powder once-daily, and a two-inhaler triple therapy containing a the fixed combination beclomethasone dipropionate, formoterol fumarate (BDP/FF 100/6 micrograms) pMDI two inhalations twice-daily and tiotropium bromide inhalation powder (TIO 18 micrograms) once-daily [BDP/FF+TIO].

At screening, the mean post-bronchodilator FEV_1 was 36.6% predicted, the mean reversibility was 7.75%, and the mean CAT score was 21.6. In the year prior to study entry, 79.7% of the patients had one moderate or severe COPD exacerbation, while 20.3% of the patients had experienced more than one exacerbation.

BDP/FF/GB demonstrated a statistically significant reduction in the annual rate of moderate/severe exacerbations (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation) compared with TIO (primary endpoint), as well as a statistically significant improvement in lung function (as defined by change from baseline in pre-dose FEV_1 at Week 52; key secondary endpoint) compared with TIO (see Table 5).

In addition, no relevant differences were observed between BDP/FF/GB and BDP/FF+TIO in terms of change from baseline in pre-dose FEV_1 at Week 52 (key secondary endpoint) and moderate/severe exacerbation rate.
BDP/FF/GB showed improvement compared with TIO at Week 52 in health-related quality of life measured by the SGRQ total score.

Table 5: Key efficacy endpoints, ITT population (Study CCD-1208-PR-0090, TRINITY)

	BDP/FF/GB 100/6/12.5 mcg (N = 1077)	TIO 18 mcg (N = 1074)	BDP/FF 100/6 mcg + TIO 18 mcg (N=538)
Primary endpoint			
Moderate/severe COPD exacerbation rate			
Adjusted exacerbation rate per patient per year (95% CI)	0.457 (0.412; 0.508)	0.571 (0.517; 0.632)	0.452 (0.389; 0.524)
Adjusted rate ratio BDP/FF/GB vs TIO (95% CI) p-value	0.773 (0.647; 0.924) 0.005		
Adjusted rate ratio BDP/FF/GB vs BDP/FF+TIO (95% CI) p-value	1.013 (0.846; 1.214) 0.887		
Key-secondary endpoint			
Change from baseline in pre-dose morning FEV_1 (L) at Week 52 (L)			
n Adjusted mean (95% CI)	985 0.082 (0.065; 0.100)	921 0.021 (0.003; 0.039)	495 0.085 (0.061; 0.110)
Adjusted mean difference BDP/FF/GB vs TIO (95% CI) p-value	0.061 (0.037; 0.086) < 0.001		
Adjusted mean difference BDP/FF/GB vs BDP/FF+TIO (95% CI) p-value	-0.003 (-0.033; 0.027) 0.852		
Secondary endpoints			
Time to first moderate/severe COPD exacerbation			
Hazard ratio BDP/FF/GB vs TIO (95% CI)	0.836 (0.723; 0.966)		
Hazard ratio BDP/FF/GB vs BDP/FF+TIO (95% CI)	1.055 (0.877; 1.269)		
FEV_1 responders[a] at Week 52			
Number of responders (%)	408 (37.9%)	295 (27.5%)	210 (39.0%)
Odds ratio BDP/FF/GB vs TIO (95% CI)	1.62 (1.35, 1.95)		
Odds ratio BDP/FF/GB vs BDP/FF+TIO (95% CI)	0.95 (0.76; 1.18)		
Change from baseline in SGRQ total score at Week 52			
n Adjusted mean (95% CI)	899 -5.74 (-6.60; -4.88)	860 -4.14 (-5.01; -3.27)	463 -7.32 (-8.51; -6.12)

Adjusted mean difference BDP/FF/GB vs TIO (95% CI)	-1.60 (-2.82; -0.38)		
Adjusted mean difference BDP/FF/GB vs BDP/FF+TIO (95% CI)	1.57 (0.10; 3.05)		
SGRQ total score responders[b] at Week 52			
Number of responders (%)	494 (45.9)	423 (39.4)	254 (47.2)
Odds ratio BDP/FF/GB vs TIO (95% CI)	1.33 (1.11; 1.59)		
Odds ratio BDP/FF/GB vs BDP/FF+TIO (95% CI)	0.91 (0.73; 1.13)		

BDP= beclomethasone diproprionate; CAT= COPD assessment test; COPD= chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; FF= formoterol fumarate; GB= glycopyrronium bromide; n= number of patients with available data; N= Number of patients in the ITT population; SGRQ= St. George's respiratory questionnaire; TIO= tiotropium.

[a] FEV_1 response = Change from baseline in pre-dose morning $FEV_1 \geq 0.100$ L

[b] SGRQ total score response = Change from baseline in total score ≤ -4

Study 3 (CCD-05993AA1-08, TRIBUTE)

The efficacy of the single-inhaler fixed triple combination of beclomethasone dipropionate, formoterol, glycopyrronium bromide (BDP/FF/GB 100/6/12.5 micrograms) pMDI administered as a two inhalations twice-daily treatment in patients with a clinical diagnosis of COPD has been evaluated in this 52-week active-controlled study compared to the fixed combination indacaterol/glycopyrronium (IND/GLY 85/43 micrograms) inhalation powder once-daily.

At screening, the mean post-bronchodilator FEV_1 was 36.4% predicted, and the mean reversibility was 8.58%. The mean CAT score was 21.2. In the year prior to study entry, 80.8% of the patients had one moderate or severe COPD exacerbation, while 19.2% of the patients experienced more than one exacerbation.

BDP/FF/GB demonstrated a statistically significant reduction in the annual rate of moderate/severe exacerbations (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation) compared with IND/GLY (primary endpoint) (see Table 6). Time to first moderate/severe COPD exacerbation, as well as the analyses of moderate and severe COPD exacerbations (considered separately) showed a trend toward a delay in time to the first event and a reduction of the rate of exacerbation.

BFP/FF/GB improved average pre-dose FEV_1 over the 52-week treatment period compared to IND/GLY. A similar improvement was observed at Week 52 (data not shown).

Treatment with BDP/FF/GB showed an improvement compared with IND/GLY in health-related quality of life measured by the SGRQ total score at Week 52.

The lung function and SGRQ total score outcomes at Week 26 were consistent with the results observed at Week 52 (data not shown).

Table 6: Key efficacy endpoints, ITT population (Study CCD-05993AA1-08, TRIBUTE)

	BDP/FF/GB 100/6/12.5 mcg (n = 764)	IND/GLY 85/43 mcg (n = 768)
Primary endpoint		
Moderate/severe COPD exacerbation rate		
Adjusted exacerbation rate per patient per year (95% CI)	0.504 (0.447; 0.569)	0.595 (0.530; 0.668)
Adjusted rate ratio (95% CI) p-value	0.848 (0.723; 0.995) 0.043	
Secondary endpoints		
Time to first moderate/severe COPD exacerbation		
Hazard ratio (95% CI)	0.901 (0.763; 1.064)	
Change from baseline in SGRQ total score at Week 52		
n Adjusted mean (95% CI)	667 -3.49 (-4.36; -2.63)	654 -1.85 (-2.72; -0.98)
Adjusted mean difference (95% CI)	-1.64 (-2.87; -0.42)	

BDP= beclomethasone dipropionate; COPD= chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; FF= formoterol fumarate; GB= glycopyrronium bromide; n= number of patients with available data; IND= indacaterol; N= Number of patients in the ITT population; SGRQ= St. George's respiratory questionnaire.

Study 4 (CCD-05993AA1-07, TRISTAR)

The effect on health-related quality of life of the single-inhaler fixed triple combination of beclomethasone dipropionate, formoterol, glycopyrronium bromide (BDP/FF/GB 100/6/12.5 micrograms) pMDI administered as a two inhalations twice-daily treatment in patients with a clinical diagnosis of COPD has been evaluated in this multicentre, randomised, open-label, parallel group, 26-week active-controlled study compared to a two-inhaler triple therapy with the fixed combination of fluticasone furoate, vilanterol (FLU/VI 92/22 micrograms) inhalation powder, pre-dispensed once-daily and tiotropium (TIO 18 micrograms) inhalation powder hard capsule once-daily.

At screening, the mean post-bronchodilator FEV_1 was 36.3% predicted, the mean reversibility was 7.27%, and the mean CAT score was 22.8. In the year prior to study entry, 84.1% of the patients had one moderate or severe COPD exacerbation, while 15.9% of the patients had experienced more than one exacerbation.

BDP/FF/GB was non-inferior to FLU/VI+TIO at Week 26 in health-related quality of life measured by the St. George's Respiratory Questionnaire (SGRQ) total score, with the upper limit of the 95% CI for the adjusted mean difference between treatments being below the non-inferiority margin of 4 units (primary endpoint). The responder analysis on the same outcome showed similar results.

No relevant differences were observed in the secondary endpoints (see Table 7).

Table 7: Key efficacy endpoints, ITT population (Study CCD-05993AA1-07, TRISTAR)

	BDP/FF/GB 100/6/12.5 mcg (n = 577)	FLU/VI 92/22 mcg + TIO 18 mcg (n = 579)
Primary endpoint		
Change from baseline in SGRQ total score at Week 26		
n Adjusted mean (95% CI)	553 -6.77 (-7.91; -5.64)	553 -7.82 (-8.95; -6.68)
Adjusted mean difference (95% CI) p-value	1.04 (-0.56; 2.65) 0.204	
Secondary endpoints		
SGRQ total score responders[a] at Week 26		
Number of responders (%)	295 (51.1%)	307 (53.0%)
Odds ratio (95% CI)	0.926 (0.728; 1.176)	
Moderate/severe COPD exacerbation rate		
Adjusted exacerbation rate per patient per year (95% CI)	0.418 (0.346; 0.506)	0.385 (0.316; 0.468)
Adjusted rate ratio (95% CI)	1.086 (0.842; 1.402)	
Change from baseline in pre-dose morning FEV_1 (L) at Week 26 (L)		
n Adjusted mean (95% CI)	553 0.057 (0.036; 0.077)	548 0.105 (0.085; 0.125)
Adjusted mean difference (95% CI)	-0.048 (-0.077; -0.020)	
FEV_1 responders[b] at Week 26		
Number of responders (%)	211 (36.6%)	248 (42.8%)
Odds ratio (95% CI)	0.75 (0.59; 0.95)	

BDP= beclomethasone dipropionate; COPD= chronic obstructive pulmonary disease; FEV_1= forced expiratory volume in 1 second; FF= formoterol fumarate; FLU= fluticasone; GB= glycopyrronium bromide; n= number of patients with available data; N= Number of patients in the ITT population; SGRQ= St. George's respiratory questionnaire; VI= vilanterol.

[a] SGRQ total score response = Change from baseline in total score ≤ -4

5.2 PHARMACOKINETIC PROPERTIES

The systemic exposure to beclometasone dipropionate, formoterol and glycopyrronium has been investigated in a pharmacokinetic study conducted in healthy subjects. The study compared data obtained after treatment with a single dose of TRIMBOW (4 inhalations of 100/6/25 micrograms, a non marketed formulation containing twice the approved strength of glycopyrronium) or a single dose of the extemporary combination of beclometasone dipropionate/formoterol (4 inhalations of 100/6 micrograms) plus glycopyrronium (4 inhalations of 25 micrograms). The maximum plasma concentration and systemic exposure of beclometasone dipropionate main active metabolite (beclometasone 17 monopropionate) and formoterol were similar after administration of the fixed or extemporary combination. For

glycopyrronium, the maximum plasma concentration was similar after administration of the fixed or extemporary combination, while the systemic exposure was slightly higher after administration of TRIMBOW than with the extemporary combination. This study also investigated the potential pharmacokinetic interaction between the active components of TRIMBOW by comparing the pharmacokinetic data obtained after a single dose of the extemporary combination or after a single dose of the single components beclometasone dipropionate/formoterol or glycopyrronium. There was no clear evidence of pharmacokinetic interaction, however the extemporary combination showed formoterol and glycopyrronium levels transiently slightly higher immediately after dosing compared with the single components. It is noted that single component glycopyrronium, formulated as pressurised metered dose inhaler, which was used in the PK studies, is not available on the market.

A comparison across studies showed that the pharmacokinetics of beclometasone 17 monopropionate, formoterol and glycopyrronium is similar in COPD patients and in healthy subjects.

Effect of a spacer
The use of TRIMBOW with the AeroChamber Plus spacer in COPD patients increased the lung delivery of beclometasone 17 monopropionate, formoterol and glycopyrronium (maximum plasma concentration increased by 15%, 58% and 60% respectively). The total systemic exposure (as measured by AUC_{0-t}) was slightly reduced for beclometasone 17 monopropionate (by 37%) and formoterol (by 24%), while it was increased for glycopyrronium (by 45%). See also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Effect of renal impairment
Systemic exposure (AUC_{0-t}) to beclometasone dipropionate, to its metabolite beclometasone 17 monopropionate and to formoterol was not affected by mild to severe renal impairment. For glycopyrronium, there was no impact in subjects with mild and moderate renal impairment. However, an increase in total systemic exposure of up to 2.5-fold was observed in subjects with severe renal impairment (glomerular filtration rate below 30 mL/min/1.73 m^2), as a consequence of a significant reduction of the amount excreted in urine (approximately 90% reduction of glycopyrronium renal clearance). Simulations performed with a pharmacokinetic model showed that even when covariates had extreme values (body weight less than 40 kg and concomitant glomerular filtration rate below 27 mL/min/1.73 m^2), exposure to TRIMBOW active substances remains in approximately a 2.5-fold range compared to the exposure in a typical patient with median covariate values.

BECLOMETASONE DIPROPIONATE
Beclometasone dipropionate is a pro-drug with weak glucocorticoid receptor binding affinity that is hydrolysed via esterase enzymes to an active metabolite beclometasone 17 monopropionate which has a more potent topical anti-inflammatory activity compared with the pro-drug beclometasone dipropionate.

Absorption, distribution and metabolism
Inhaled beclometasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to beclometasone 17 monopropionate via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung

(36%) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed beclometasone dipropionate is negligible; however, pre-systemic conversion to beclometasone 17 monopropionate results in 41% of the dose being absorbed as the active metabolite. There is an approximately linear increase in systemic exposure with increasing inhaled dose. The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged beclometasone dipropionate and beclometasone 17 monopropionate respectively. Following intravenous dosing, the disposition of beclometasone dipropionate and its active metabolite is characterised by high plasma clearance (150 and 120 L/h respectively), with a small volume of distribution at steady state for beclometasone dipropionate (20 L) and larger tissue distribution for its active metabolite (424 L). Plasma protein binding is moderately high.

Excretion

Faecal excretion is the major route of beclometasone dipropionate elimination mainly as polar metabolites. The renal excretion of beclometasone dipropionate and its metabolites is negligible. The terminal elimination half-lives are 0.5 hours and 2.7 hours for beclometasone dipropionate and beclometasone 17 monopropionate, respectively.

Patients with hepatic impairment

The pharmacokinetics of beclometasone dipropionate in patients with hepatic impairment has not been studied, however, as beclometasone dipropionate undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs and liver to form the more polar products beclometasone 21 monopropionate, beclometasone 17 monopropionate and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of beclometasone dipropionate.

FORMOTEROL

Absorption and distribution

Following inhalation, formoterol is absorbed from both the lung and the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of the unchanged active substance occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 micrograms of formoterol.

Metabolism

Formoterol is widely metabolised, and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

Excretion

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12 96 micrograms dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 micrograms dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged active substance excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing. After oral administration (40 to 80 micrograms), 6% to 10% of the dose was recovered in urine as unchanged active substance in healthy subjects; up to 8% of the dose was recovered as the glucuronide. A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 mL/min.

Patients with hepatic impairment

The pharmacokinetics of formoterol has not been studied in patients with hepatic impairment; however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

GLYCOPYRRONIUM

Absorption and distribution

Glycopyrronium has a quaternary ammonium structure which limits its passage across biological membranes and produces slow, variable and incomplete gastrointestinal absorption. Following glycopyrronium inhalation, the lung bioavailability was 10.5% (with activated charcoal ingestion) while the absolute bioavailability was 12.8% (without activated charcoal ingestion) confirming the limited gastrointestinal absorption and indicating that more than 80% of glycopyrronium systemic exposure was from lung absorption. After repeated inhalation of twice daily doses ranging from 12.5 to 50 micrograms via pressurised metered dose inhaler in COPD patients, glycopyrronium showed linear pharmacokinetics with little systemic accumulation at steady state (median accumulation ratio 2.2 2.5). The apparent volume of distribution (Vz) of inhaled glycopyrronium was increased compared to intravenous (i.v.) infusion (6420 L versus 323 L), reflecting the slower elimination after inhalation.

Metabolism

The metabolic pattern of glycopyrronium in vitro (humans, dogs, rats, mice and rabbits liver microsomes and hepatocytes) was similar among species and the main metabolic reaction was the hydroxylation on the phenyl or ciclopentyl rings. CYP2D6 was found to be the only enzyme responsible for glycopyrronium metabolism.

Excretion

The mean elimination half-life of glycopyrronium in healthy volunteers was approximately 6 hours after i.v. injection while after inhalation in COPD patients it ranged from 5 to 12 hours at steady state. After a glycopyrronium single i.v. injection, 40% of the dose was excreted in the urine within 24 hours. In COPD patients receiving repeated twice daily administration of inhaled glycopyrronium, the fraction of the dose excreted in urine ranged from 13.0% to 14.5%

at steady state. Mean renal clearance was similar across the range of doses tested and after single and repeated inhalation (range 281 396 mL/min).

5.3 PRECLINICAL SAFETY DATA

GENOTOXICITY

Individually, beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide were devoid of genotoxic activity in assays for bacterial mutagenicity, chromosomal aberrations in vitro (human lymphocytes) and in vivo clastogenicity (rat bone marrow micronucleus test).

CARCINOGENICITY

Carcinogenicity studies have not been performed with beclometasone dipropionate, formoterol fumarate and glycopyrronium bromide in combination. Data for the individual active components are described below:

Beclometasone dipropionate: The potential carcinogenicity of beclometasone dipropionate has not been adequately investigated in animal studies. Other glucocorticoids (budesonide, prednisolone and triamcinolone acetate) have been shown to increase the incidence of hepatocellular tumours in rats by a non-genotoxic mechanism.

Formoterol fumarate: In 2-year studies in mice and rats, treatment with formoterol fumarate, given via the diet or drinking water at very high doses, was associated with increases in several tumour types. In mice, these included hepatocellular adenoma and carcinomas (≥2 mg/kg/day), leiomyomas and leiomyosarcomas in the female reproductive tract (≥2 mg/kg/day) and adrenal subcapsular cell tumours (≥66 mg/kg/day). In rats, treatment was associated with benign granulosa/theca cell tumours in the ovaries (≥0.5 mg/kg/day), mesovarian leiomyomas (≥18 mg/kg/day), mammary adenocarcinomas (≥36 mg/kg/day) and thyroid C-cell neoplasms (46 mg/kg/day). A mesovarian leiomyoma was also observed in a female rat dosed by inhalation at 130 μg/kg/day for two years (almost 60 times the maximum recommended human dose for TRIMBOW, adjusted for body surface area). Mammary adenocarcinomas, smooth muscle tumours in the female reproductive tract and effects on the ovary have been reported in rats and mice treated with other β2-adrenergic agonists and are likely to be secondary to prolonged stimulation of β2-adrenoceptors in these tissues.

Glycopyrronium bromide: No carcinogenic activity was observed for glycopyrronium bromide in a 26-week oral study in transgenic (rasH2) mice and a 2-year inhalational study in rats. The highest dose levels employed (150 mg/kg/day in mice and 447 μg/kg/day in rats) yielded systemic exposure (plasma AUC) levels to glycopyrronium approximately 70–320 times higher in mice and 140 times higher in rats than in humans at the maximum recommended clinical dose of TRIMBOW."

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ethanol absolute
Hydrochloric acid

Norflurane (propellant)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Prior to dispensing:
Store in a refrigerator (2-8°C) for a maximum of 18 months. Do Not Freeze.

After dispensing:
Store below 30°C (for a maximum of 2 months).

6.5 NATURE AND CONTENTS OF CONTAINER
Pressurised container (coated aluminium), with a metering valve. The pressurised container is inserted in a polypropylene inhaler which incorporates a mouthpiece and a dose counter (120 actuations per pressurised container) and is provided with a polypropylene mouthpiece cap.

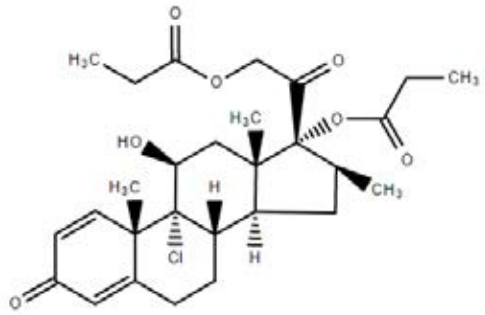
Each pack contains one pressurised container which provides 120 actuations.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
For pharmacists:

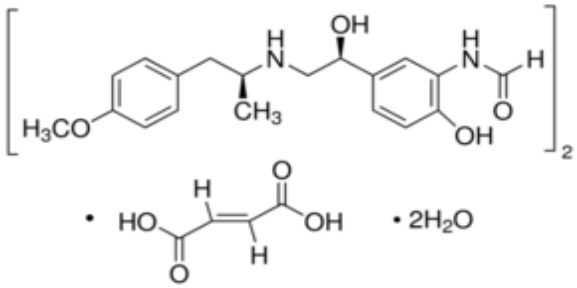
Enter the date of dispensing to the patient on the pack.

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

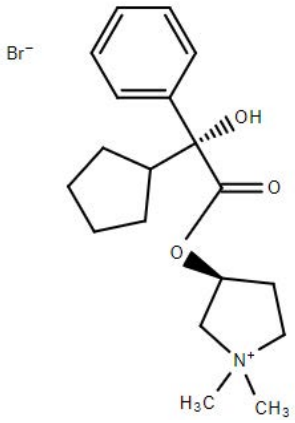
6.7 PHYSICOCHEMICAL PROPERTIES
Chemical structure



Beclometasone dipropionate



Formoterol (eformoterol) fumarate dihydrate



Glycopyrronium bromide (glycopyrrolate)

CAS number
Beclometasone dipropionate: 5534-09-8
Formoterol fumarate dihydrate: 183814-30-4
Glycopyrronium: 596-51-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription only medicine)

8. SPONSOR

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9. DATE OF FIRST APPROVAL

24 June 2020

10. DATE OF REVISION

24 June 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information