

AUSTRALIAN PRODUCT INFORMATION
TRIMBOW 100/6/10 and 200/6/10
(beclometasone dipropionate, formoterol fumarate dihydrate and
glycopyrronium [as bromide])
pressurised inhalation

1. NAME OF THE MEDICINE

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIMBOW 100/6/10

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

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).

TRIMBOW 200/6/10

Each metered dose (the dose leaving the valve) contains 200 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (equivalent to 12.5 micrograms of glycopyrronium bromide).

Each delivered dose (the dose leaving the mouthpiece) contains 172 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (equivalent to 11 micrograms glycopyrronium bromide).

Excipient with known effect: ethanol absolute.

For the full list of excipients see section [6.1 LIST OF EXCIPIENTS](#).

3. PHARMACEUTICAL FORM

Pressurised inhalation.

Colourless to yellowish liquid solution.

The inhalation solution is contained in a pressurised aluminium container sealed with a metering valve (pressurised metered dose inhaler (pMDI)). 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 (TRIMBOW 100/6/10) or green cap (TRIMBOW 200/6/10). The actuator has a dose counter.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

COPD

TRIMBOW 100/6/10 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).

Asthma

TRIMBOW 100/6/10

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta₂-agonist and medium dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

TRIMBOW 200/6/10

Maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting beta₂-agonist and high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 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.

Patients should be advised to take TRIMBOW every day even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be used for immediate relief.

Asthma

When choosing the starting dose strength of TRIMBOW 100/6/10 or TRIMBOW 200/6/10, the patients' disease severity, their previous asthma therapy including the inhaled corticosteroid (ICS) dose as well as the patients' current control of asthma symptoms and risk of future exacerbation should be considered.

Stepping-down treatment

Patients should be regularly reassessed by a doctor, so that their doses of TRIMBOW remain optimal and are only changed on medical advice. The doses should be titrated to the lowest doses at which effective control of asthma symptoms is maintained.

There are no data on the effect of stepping-down from the high strength (TRIMBOW 200/6/10) to the medium strength beclometasone dipropionate medicinal product (TRIMBOW 100/6/10).

Special populations

Paediatric population

COPD

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

Asthma

The safety and efficacy of TRIMBOW in the paediatric population (under 18 years of age) have not yet been established. No data available.

Elderly

No dose 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 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.

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 (see [Instructions for use](#)).

TRIMBOW is provided with a dose counter or dose indicator on the back of the inhaler, which shows how many actuations remain. For the 60 and 120 actuation pressurised containers, each time the patient presses the container a puff of the solution is released and the counter counts down by

one.

For the 180 actuation pressurised container, each time the patient presses the pressurised container a puff of the solution is released and the indicator rotates by a small amount. The number of actuations remaining is displayed in intervals of 20.

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

Instructions for use

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 (primed for use). Before priming the 60, 120 or 180 actuation pressurised containers, the counter/indicator should read 61, 121 or 180, respectively. After priming, the counter/indicator should read 60, 120 or 180.

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.

Patients should rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling (see 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 actuations 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. 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 a suitable spacer device, properly cleaned as described in the relevant spacer 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 a suitable spacer with one continuous slow and deep breath. Any delays between actuation and inhalation should be kept to a minimum. Alternatively, patients may simply breathe in and out (through the mouth) after the actuation, as instructed in the spacer leaflet, to obtain the medicinal product. (See section [4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE](#) and section [5.2 PHARMACOKINETIC PROPERTIES](#)).

Use with a spacer

Single dose pharmacokinetic data (see section [5.2 PHARMACOKINETIC PROPERTIES](#)) have demonstrated that in comparison to routine use without a spacer device, the use of TRIMBOW with the AeroChamber Plus spacer device increased the total systemic exposure (AUC_{0-t}) to glycopyrronium. However, available safety data from long-term clinical studies have not raised any significant safety concerns (see section [5.1 PHARMACODYNAMIC PROPERTIES](#) and section [5.2 PHARMACOKINETIC PROPERTIES](#)).

Cleaning

For the regular cleaning of the inhaler, patients should remove the cap from the mouthpiece weekly and wipe the outside and inside of the mouthpiece with a dry cloth. They should not remove the canister 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 disease exacerbation (i.e. as a rescue therapy).

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration. 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, treatment 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). Treatment should be discontinued immediately, the patient assessed, and alternative therapy instituted if necessary.

Deterioration of disease

It is recommended that treatment 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 or progressive deterioration in symptoms is potentially life-threatening and the patient should undergo urgent medical assessment.

Cardiovascular effects

Due to the presence of a long acting beta₂-agonist and a long acting muscarinic antagonist TRIMBOW should be used with caution in patients with cardiac arrhythmias, especially third-degree atrioventricular block and tachyarrhythmias (accelerated and/or irregular heartbeat, including atrial fibrillation), 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. Patients diagnosed with the described cardiovascular conditions were excluded from clinical trials with TRIMBOW. Limited data in asthmatic patients with cardiovascular co-morbidities or risk-factors suggest that these patients are also at higher risk of adverse reactions like local fungal infections or dysphonia (see section [4.8 ADVERSE EFFECTS \(UNDESIRABLE EFFECTS\)](#)).

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 treating 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. Evidence for an intra-class difference in the pneumonia risk has been generated in an historical cohort study, comparing pneumonia risk in patients initiating fixed dose combination (FDC) beclometasone with those initiating FDC fluticasone in patients with COPD with the risk being greater in the FDC fluticasone group (see [section 5.1 PHARMACODYNAMIC PROPERTIES](#)).

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, 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, and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained (see section [4.2 DOSE AND METHOD OF ADMINISTRATION](#)).

TRIMBOW should be administered with caution in patients with active or quiescent pulmonary tuberculosis, and in patients with 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 treatment 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 with other anticholinergic-containing medicinal products is not recommended (see section [4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS](#)).

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.

Stepping-down treatment

Patients should be regularly reassessed by a doctor, so that their doses of TRIMBOW remain optimal and are only changed on medical advice. The doses should be titrated to the lowest doses at which effective control of asthma symptoms is maintained.

Excipients

TRIMBOW contains a small amount of ethanol absolute (i.e. 8.856 mg of ethanol per actuation, which is equivalent to 17.712 mg per dose of two actuations).

There is a theoretical potential for interaction in particularly sensitive patients taking disulfiram or metronidazole.

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 patients with severe disease 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](#)).

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 β_2 -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 should be observed for adrenal suppression.

If treatment during pregnancy is necessary, the lowest effective dose should be used (see section [4.2 DOSE AND METHOD OF ADMINISTRATION](#)).

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. Anticholinergics 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

COPD

The most frequently reported adverse events in the three Phase III, 52 week active-controlled studies in COPD using beclometasone dipropionate, formoterol fumarate, glycopyrronium bromide (BDP/FF/GB 100/6/12.5) from the TRILOGY, TRINITY and TRIBUTE studies are presented in [Table 1](#), [Table 2](#) and [Table 3](#).

The TRILOGY study 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.

The TRINITY study 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. The third arm included 537 patients with COPD treated with a two-inhaler triple therapy consisting of a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms (corresponding to a delivered dose of 84.6/5.0 micrograms) pMDI two inhalations twice daily plus tiotropium bromide 18 micrograms inhalation powder, hard capsule, once daily.

The TRIBUTE study included 764 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 768 patients with COPD treated with an active comparator, indacaterol/glycopyrronium 110/50 micrograms inhalation powder, hard capsule, once daily.

Table 1. Adverse events with $\geq 1\%$ incidence with TRIMBOW in TRILOGY clinical trial

System Organ Class, Preferred Term	BDP/FF/GB 400/24/50 mcg [#] N=687 Number of patients (%)	BDP/FF 400/24 mcg [#] N=680 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%)
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%)

System Organ Class, Preferred Term	BDP/FF/GB 400/24/50 mcg [#] N=687 Number of patients (%)	BDP/FF 400/24 mcg [#] N=680 Number of patients (%)
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 $\geq 1\%$ incidence with TRIMBOW in TRINITY clinical trial.

System Organ Class, Preferred Term	BDP/FF/GB 400/24/50 mcg [#] N=1077 Number of patients (%)	Tiotropium 18 mcg [#] N=1076 Number of patients (%)	BDP/FF 400/24 μ g + Tiotropium 18 mcg [#] N=537 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			
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.

Table 3. Adverse events with ≥1% incidence with TRIMBOW in TRIBUTE clinical trial

System Organ Class, Preferred Term	BDP/FF/GB 400/24/50 mcg [#] N=764	IND/GB 110/50 mcg [#] N=768
	Number of patients (%)	Number of patients (%)
Cardiac disorders		
Atrial fibrillation	5 (0.7%)	10 (1.3%)
Cardiac failure	9 (1.2%)	7 (0.9%)
Gastrointestinal disorders		
Diarrhoea	8 (1.0%)	8 (1.0%)
Abdominal distension	8 (1.0%)	5 (0.7%)
Toothache	5 (0.7%)	13 (1.7%)
Infections and infestations		
Nasopharyngitis	43 (5.6%)	37 (4.8%)
Pneumonia*	28 (3.7%)	27 (3.5%)
Respiratory tract infection viral	9 (1.2%)	9 (1.2%)
Upper respiratory tract infection	11 (1.4%)	11 (1.4%)
Oral candidiasis	13 (1.7%)	5 (0.7%)
Influenza	8 (1.0%)	6 (0.8%)
Bronchitis	9 (1.2%)	6 (0.8%)
Viral infection	12 (1.6%)	7 (0.9%)
Metabolism and nutrition disorders		
Diabetes mellitus	6 (0.8%)	10 (1.3%)
Musculoskeletal and connective tissue disorders		
Arthralgia	10 (1.3%)	11 (1.4%)
Pain in extremity	1 (0.1%)	10 (1.3%)
Back pain	21 (2.7%)	23 (3.0%)
Nervous system disorders		
Headache	44 (5.8%)	35 (4.6%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease	273 (35.7%)	288 (37.5%)
Dyspnoea	21 (2.7%)	21 (2.7%)
Cough	13 (1.7%)	21 (2.7%)
Rhinitis	7 (0.9%)	13 (1.7%)
Vascular disorders		
Hypertension	15 (2.0%)	22 (2.9%)

BDP/FF/GB = beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide (TRIMBOW)

Indacaterol/GB = glycopyrronium bromide

*Includes the preferred terms of bronchopneumonia, interstitial lung disease, lobar pneumonia, pneumonia, pneumonia bacterial, pneumonia streptococcal, pneumonia viral and pulmonary tuberculosis

[#]Total daily dose

Summary of the safety profile

The most frequently reported adverse reactions in patients with COPD or asthma with TRIMBOW were respectively: dysphonia (0.3% and 1.5%) and oral candidiasis (0.8% and 0.3%), which are normally associated with ICS; muscle spasms (0.4% and 0.2%), which can be attributed to the LABA component; and dry mouth (0.4% and 0.5%), which is a typical anticholinergic effect, which can be attributed to the LAMA component.

In asthmatic patients, adverse reactions tend to cluster during the first 3 months following initiation of therapy and become less frequent with longer-term use (after 6 months of treatment).

Tabulated list of adverse reactions

Adverse reactions associated with TRIMBOW occurred during clinical trials and post-marketing experience as well as adverse reactions listed for the marketed individual components are provided in [Table 4](#), listed by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from available data).

Table 4. Adverse reactions with TRIMBOW*

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

MedDRA system organ class	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	Uncommon	Rash ¹ , urticaria ¹ , pruritus, hyperhidrosis ¹
	Rare	Angioedema ¹
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms, myalgia, pain in extremity ¹ , musculoskeletal chest pain ¹
	Very rare	Growth retardation ¹
Renal and urinary disorders	Rare	Dysuria, urinary retention, nephritis ¹
General disorders and administration site conditions	Uncommon	Fatigue ¹
	Rare	Asthenia
	Very rare	Oedema peripheral ¹
Investigations	Uncommon	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
	Rare	Blood pressure increased ¹ , blood pressure decreased ¹
	Very rare	Bone density decreased ¹

*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

¹Adverse reactions reported in the product information 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 13 11 26 (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 (BDP/FF/GB) in a non-volatile solution formulation and uses a specific actuator orifice geometry (MODULITE[®] technology) which results 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. 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. 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

COPD

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 FEV₁/FVC ratio <0.70 and FEV₁ 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 (TRILOGY)

The efficacy of the single-inhaler fixed triple combination of beclometasone 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 - beclometasone dipropionate, formoterol fumarate (BDP/FF 100/6 micrograms) two inhalations twice-daily.

At screening, the mean post-bronchodilator FEV₁ 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 FEV₁ at Week 26 and change from baseline in 2-hour post-dose FEV₁; co-primary endpoints) compared with BDP/FF (see [Table 5](#)).

BDP/FF/GB showed a numerical improvement compared with BDP/FF at Week 26 for dyspnoea severity measured by the transition dyspnoea 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 5](#)).

The lung function, TDI and SGRQ outcomes at Week 52 (data not shown) were consistent with the results observed at Week 26 (see [Table 5](#)).

Table 5. Key efficacy endpoints, ITT population (TRILOGY)

	BDP/FF/GB 100/6/12.5 mcg (n = 687)	BDP/FF 100/6 mcg (n = 680)
Primary endpoints		
<i>Change from baseline in pre-dose morning FEV₁ (L) at Week 26 (L)</i>		
N	642	616
Adjusted mean (95% CI)	0.082 (0.062; 0.102)	0.001 (-0.019; 0.021)
Adjusted mean difference (95% CI)	0.081 (0.052; 0.109)	
p-value	< 0.001	
<i>Change from baseline in 2-hour post-dose FEV₁ (L) at Week 26 (L)</i>		
n	631	609
Adjusted mean (95% CI)	0.261 (0.240; 0.283)	0.145 (0.123; 0.166)
Adjusted mean difference (95% CI)	0.117 (0.086; 0.147)	
p-value	< 0.001	
<i>TDI focal score at Week 26</i>		
n	642	609
Adjusted mean (95% CI)	1.71 (1.50; 1.92)	1.50 (1.29; 1.71)
Adjusted mean difference (95% CI)	0.21 (-0.08; 0.51)	
p-value	0.160	

	BDP/FF/GB 100/6/12.5 mcg (n = 687)	BDP/FF 100/6 mcg (n = 680)
Secondary endpoints		
<i>Change from baseline in pre-dose morning FEV₁ (L) at Week 52 (L)</i>		
n	606	578
Adjusted mean (95% CI)	0.071 (0.050; 0.093)	0.008 (-0.014; 0.030)
Adjusted mean difference (95% CI)	0.063 (0.032; 0.094)	
<i>Change from baseline in 2-hour post-dose FEV₁ (L) at Week 52 (L)</i>		
n	598	575
Adjusted mean (95% CI)	0.249 (0.226; 0.273)	0.146 (0.122; 0.170)
Adjusted mean difference (95% CI)	0.103 (0.069; 0.137)	
<i>TDI focal score at Week 52</i>		
n	608	579
Adjusted mean (95% CI)	2.03 (1.81; 2.25)	1.81 (1.59; 2.04)
Adjusted mean difference (95% CI)	0.21 (-0.10; 0.53)	
<i>Moderate/severe COPD exacerbation rate</i>		
Adjusted exacerbation rate perpatient 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 = beclometasone dipropionate; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FEV₁ = 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 (TRINITY)

The efficacy of the single-inhaler fixed triple combination of beclometasone 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 the fixed combination beclometasone 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 FEV₁ 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 FEV₁ at Week 52; key secondary endpoint) compared with TIO (see [Table 6](#)).

In addition, no relevant differences were observed between BDP/FF/GB and BDP/FF+TIO in terms of change from baseline in pre-dose FEV₁ 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 6. Key efficacy endpoints, ITT population (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 FEV₁ (L) at Week 52 (L)			
n	985	921	495
Adjusted mean (95% CI)	0.082 (0.065; 0.100)	0.021 (0.003; 0.039)	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)		
FEV₁ 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	899	860	463
Adjusted mean (95% CI)	-5.74 (-6.60; -4.88)	-4.14 (-5.01; -3.27)	-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 = beclometasone dipropionate; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; FEV₁ = 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 FEV₁ response = Change from baseline in pre-dose morning FEV₁ ≥ 0.100 L

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

Study 3 (TRIBUTE)

The efficacy of the single-inhaler fixed triple combination of beclometasone 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 110/50 micrograms) inhalation powder once-daily.

At screening, the mean post-bronchodilator FEV₁ 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 7). 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.

BDP/FF/GB improved average pre-dose FEV₁ 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 7. Key efficacy endpoints, ITT population (TRIBUTE)

	BDP/FF/GB 100/6/12.5 mcg (n = 764)	IND/GLY 110/50 mcg (n = 768)
Primary endpoint		
<i>Moderate/severe COPD exacerbation rate</i>		
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)	0.848 (0.723; 0.995)	
p-value	0.043	
Secondary endpoints		
<i>Time to first moderate/severe COPD exacerbation</i>		
Hazard ratio (95% CI)	0.901 (0.763; 1.064)	
<i>Change from baseline in SGRQ total score at Week 52</i>		
n	667	654
Adjusted mean (95% CI)	-3.49 (-4.36; -2.63)	-1.85 (-2.72; -0.98)
Adjusted mean difference (95% CI)	-1.64 (-2.87; -0.42)	

BDP = beclometasone dipropionate; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FF = formoterol fumarate; GB = glycopyrronium bromide; GLY = glycopyrronium; 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 (TRISTAR)

The effect on health-related quality of life of the single-inhaler fixed triple combination of beclometasone 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 FEV₁ 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 8](#)).

Table 8. Key efficacy endpoints, ITT population (TRISTAR)

	BDP/FF/GB 100/6/12.5 mcg (n = 577)	FLU/VI 92/22 mcg + TIO 18 mcg (n = 579)
Primary endpoint		
<i>Change from baseline in SGRQ total score at Week 26</i>		
n	553	553
Adjusted mean (95% CI)	-6.77 (-7.91; -5.64)	-7.82 (-8.95; -6.68)
Adjusted mean difference (95% CI)	1.04 (-0.56; 2.65)	
p-value	0.204	
Secondary endpoints		
<i>SGRQ total score responders^a at Week 26</i>		
Number of responders (%)	295 (51.1%)	307 (53.0%)
Odds ratio (95% CI)	0.926 (0.728; 1.176)	
<i>Moderate/severe COPD exacerbation rate</i>		
Adjusted exacerbation rate perpatient 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)	
<i>Change from baseline in pre-dose morning FEV₁ (L) at Week 26 (L)</i>		
n	553	548
Adjusted mean (95% CI)	0.057 (0.036; 0.077)	0.105 (0.085; 0.125)
Adjusted mean difference (95% CI)	-0.048 (-0.077; -0.020)	
<i>FEV₁ responders^b at Week 26</i>		
Number of responders (%)	211 (36.6%)	248 (42.8%)
Odds ratio (95% CI)	0.75 (0.59; 0.95)	

BDP = beclometasone dipropionate; COPD = chronic obstructive pulmonary disease; FEV₁ = 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

Post-marketing experience

An historical cohort study which analysed the primary care data of patients from the OPCRCD (a real world database in the UK), was conducted to examine the risk of inhaled corticosteroid (ICS) related pneumonia, both to determine the magnitude of inter-class difference in ICS (BDP versus fluticasone propionate/fluticasone furoate), and to compare the pneumonia risk of fixed dose combination (FDC) containing BDP (either TRIMBOW or FOSTAIR) with a LABD alone. COPD patients with at least 1 year of continuous data who initiated pMDI were propensity matched (PSM) resulting in a robust study population of 13,316 for the comparison of intra-class difference (6,658 initiating FDC BDP and 6,658 initiating FDC fluticasone), and from a population of 23,898 PSM patients for the comparison of FDC BDP to LABD without an ICS (11,949 initiating FDC BDP and 11,494 initiating a LABD).

The study included both a sensitive (physician diagnosed) and specific (physician diagnosed confirmed with chest x-ray) definition of pneumonia. In the 'as-treated' PSM analysis, the study showed that initiation of FDC with fine particle fluticasone was associated with a 38% increased risk of pneumonia (sensitive definition, HR 1.38, 95% CI 1.14-1.68) and a 31% increased risk of pneumonia (specific definition, HR 1.31, 95% CI 1.05-1.62) compared with initiation of FDC extrafine BDP.

In the comparison with LABD, initiation of FDC BDP was not associated with any significant increase in pneumonia risk, based on HR 0.89, 95% CI 0.78-1.02 for the sensitive definition and HR 0.91, 95% CI 0.78-1.05 for the specific definition. In this analysis the probability for remaining pneumonia free 1- year after treatment initiation was 98.4% for FDC BDP which was comparable to the 97.7% for LABD, which was sustained for up to 6 years.

Asthma

The Phase III clinical development programme in asthma included two randomised, double-blind, active-controlled studies of 52 weeks duration, one performed with the medium ICS dose strength (BDP/FF/GB 100/6/12.5; TRIMARAN) and another one with the high ICS dose strength (BDP/FF/GB 200/6/12.5; TRIGGER).

Both studies were conducted in adult patients with a clinical diagnosis of asthma who were uncontrolled on dual maintenance treatment using a medium dose (TRIMARAN) or high dose (TRIGGER) ICS/LABA combination (ACQ-7 score ≥ 1.5). In order to be eligible, patients had to have experienced at least one asthma exacerbation requiring treatment with systemic corticosteroids or emergency department visit or in-patient hospitalisation in the previous year.

The TRIMARAN study compared two twice-daily doses of BDP/FF/GB100/6/12.5 (N=579) with two twice-daily doses of a fixed combination of beclometasone dipropionate (BDP) and formoterol (FF) 100/6 micrograms (delivered dose of 84.6/5.0) (N=576). The TRIGGER study compared two twice-daily doses of BDP/FF/GB 200/6/12.5 (N=573) with two twice-daily doses of a fixed combination of BDP and FF 200/6 micrograms alone (delivered dose 177.7/5.1) (N=576) or on top of two once-daily doses of tiotropium 2.5 micrograms (N=288) as an open-label triple combination arm.

The primary objective of the studies was to demonstrate superiority of either BDP/FF/GB 100/6/12.5 or BDP/FF/GB 200/6/12.5 (two inhalations twice daily) over the respective fixed dual combination product (medium or high dose ICS/LABA) in terms of the co-primary endpoints (change from baseline in pre-dose FEV₁ at Week 26 and the rate of moderate and severe exacerbation rate over 52 weeks).

The TRIGGER study was not powered to evaluate the comparative efficacy of BDP/FF/GB 200/6/12.5 vs. BDP/FF + tiotropium 2.5 micrograms. Descriptive results are included in [Table 9](#).

Median age of patients enrolled in the two pivotal trials was 54 years. Less than 20% of patients were aged 65 years or more and approximately 60% of patients were female. During the study, about 16% (TRIMARAN) and 23% (TRIGGER) of patients used an AeroChamber Plus spacer.

Reduction of asthma exacerbations

In the TRIMARAN study, BDP/FF/GB 100/6/12.5 significantly reduced the rate of moderate/severe exacerbations compared with the fixed combination of BDP/FF 100/6 micrograms (adjusted rate ratio 0.846, 95%CI [0.725; 0.987]).

In the TRIGGER study, BDP/FF/GB 200/6/12.5 also reduced the rate of moderate/severe exacerbations more than the fixed combination of BDP/FF 200/6 micrograms but this effect did not achieve statistical significance (adjusted rate ratio 0.880, 95%CI [0.751;1.030], p=0.11). Due to the hierarchical testing, all TRIGGER efficacy endpoints and the pre-specified analysis of severe exacerbations (data pooled across TRIMARAN and TRIGGER studies) resulted in nominal p-values only ([Table 9](#)).

Data of TRIMARAN and TRIGGER studies suggest that the time to first moderate/severe exacerbation (secondary endpoint) was prolonged in the triple combination arm when compared with the respective dual combination arm.

Effects on lung function

In both studies, BDP/FF/GB 100/6/12.5 and BDP/FF/GB 200/6/12.5 improved the lung function parameters of pre-dose FEV₁ (co-primary endpoint), peak0-3h FEV₁, and morning peak expiratory flow (key secondary endpoints), compared with a fixed combination of beclometasone dipropionate

and formoterol 100/6 micrograms and 200/6 micrograms, respectively, after 26 weeks of treatment. All improvements were statistically significant (see Table 9).

Table 9. Results of primary and secondary endpoints

Study	TRIMARAN	TRIGGER	
Comparison of interest	BDP/FF/GB 100/6/12.5 (N=579)	BDP/FF/GB 200/6/12.5 (N=573)	BDP/FF/GB 200/6/12.5 (N=573)
N = randomised patients per treatment arm	vs BDP/FF¹ 100/6 N=576)	vs BDP/FF¹ 200/6 (N=576)	vs BDP/FF¹ 200/6+ tiotropium 2.5² (N=288)
Primary endpoints			
Pre-dose FEV₁ after 26 weeks (co-primary endpoint)			
Treatment difference	+57 mL	+73 mL	-45 mL
p-value	p = 0.008	p = 0.003*	p = 0.125*
Moderate/severe exacerbations over 52 weeks (co-primary endpoint)			
Adjusted rate per patient/year	1.83 vs 2.16	1.73 vs 1.96	1.73 vs 1.63
Rate change	-15.4%	-12.0%	+7.0%
p-value	p = 0.033	p = 0.110 (n.s.)	p = 0.502*
Key secondary and secondary endpoints			
Peak_{0-3h} FEV₁ after 26 weeks (key secondary endpoint)			
Treatment difference	+84 mL	+105 mL	-33 mL
p-value	p < 0.001	p < 0.001*	p = 0.271*
Morning peak expiratory flow (PEF) over 26 weeks (key secondary endpoint)			
Treatment difference	+8 L/min	+8 L/min	-0.2 L/min
p-value	p < 0.001	p = 0.001*	p = 0.951*
Rate of severe exacerbations over 52 weeks, pooled analysis (key secondary endpoint)			
Adjusted rate per patient/year	0.24 vs 0.31		n. a.
Rate change	-23.0%		
p-value	p = 0.008*		
Time to the first moderate/severe exacerbation over 52 weeks (secondary endpoint)			
Hazard ratio	0.84	0.80	1.03
p-value	p = 0.022*	p = 0.003*	p = 0.777*
Time to the first severe exacerbation over 52 weeks, pooled analysis (secondary endpoint)			
Hazard ratio	0.79		n.a.
p-value	p = 0.011*		

n.a. = not applicable

n.s. = not statistically significant

¹ = fixed combination of beclometasone dipropionate (BDP) plus formoterol fumarate (FF)

² = open-label group

* = nominal p-values

Co-primary endpoints (pre-dose FEV₁ at Week 26 and the rate of moderate and severe exacerbation rate over 52 weeks) and the key secondary endpoints (peak_{0-3h} FEV₁ at Week 26, morning PEF over 26 weeks and the rate of severe exacerbations [pooled analysis of TRIMARAN and TRIGGER] over 52 weeks) were part of the step-down, closed confirmatory testing strategy and thus controlled for multiplicity.

Since the superiority test of one of the co-primary endpoints in the TRIGGER study did not achieve statistical significance, results for TRIGGER efficacy endpoints and the rate of severe exacerbations

(pooled analysis) are nominal p-values and presented for descriptive purposes.

Since the TRIGGER trial was not powered to evaluate the comparative efficacy of BDP/FF/GB 200/6/12.5 vs. BDP/FF 200/6 plus tiotropium 2.5, it is not clear whether the observed differences are real or a random result.

5.2 PHARMACOKINETIC PROPERTIES

TRIMBOW - fixed combination

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 extemporaneous 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 extemporaneous combination. For glycopyrronium, the maximum plasma concentration was similar after administration of the fixed or extemporaneous combination, while the systemic exposure was slightly higher after administration of TRIMBOW than with the extemporaneous 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 extemporaneous 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 extemporaneous 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.

The dose proportionality of systemic and lung exposure to beclometasone dipropionate has been investigated in a pharmacokinetic study conducted in healthy subjects with non-marketed TRIMBOW. The study compared data obtained after treatment with a single dose (4 inhalations) of TRIMBOW 200/6/25 micrograms or a single dose (4 inhalations) of TRIMBOW 100/6/25 micrograms (both are non-marketed formulations containing twice the approved strength of glycopyrronium). TRIMBOW 200/6/25 micrograms treatment resulted in a two times higher systemic and lung exposure to beclometasone dipropionate and to its main active metabolite (beclometasone 17-monopropionate) in comparison to TRIMBOW 100/6/25 micrograms, which is consistent with the different strengths of the two formulations. The systemic and lung exposure to glycopyrronium and formoterol was similar after the two treatments, although a high variability was observed for glycopyrronium bromide C_{max} .

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

Effect of a spacer

In patients with COPD the use of TRIMBOW with the AeroChamber Plus spacer 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.

In patients with asthma, the use of TRIMBOW with a spacer increased the lung delivery of beclometasone 17-monopropionate, formoterol and glycopyrronium (maximum plasma concentration increased by 7%, 23% and 34% respectively). The total systemic exposure (as measured by AUC_{0-t}) was slightly reduced for beclometasone 17-monopropionate (by 34%) and formoterol (by 30%), while it was increased for glycopyrronium (by 36%). (See section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 m²), 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 m²), 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 (V_z) 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 cyclopentyl 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 $\mu\text{g}/\text{kg}/\text{day}$ 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 β_2 -adrenergic agonists and are likely to be secondary to prolonged stimulation of β_2 -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 $\mu\text{g}/\text{kg}/\text{day}$ 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 (CFC-free propellant also known as HFA-134a)

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

Store at 2°C to 8°C (Refrigerate. Do not freeze).

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

Advise the patient to enter the date of first use on the removable label and affix to the actuator.

TRIMBOW 200/6/10 pack containing 60 actuations only:

After first use: Store below 30°C (for a maximum of 1 month).

Advise the patient to enter the date of first use on the removable label and affix to the actuator.

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 (60 or 120 actuations) or dose indicator (180 actuations) with a polypropylene mouthpiece cap.

TRIMBOW 100/6/10 pack sizes:

Single inhaler pack containing either 60, 120 or 180 actuations.
Multiple packs containing 2 or 3 inhalers each with 120 actuations.

TRIMBOW 200/6/10 pack sizes:

Single inhaler pack containing either 60 or 120 actuations.
Multiple packs containing 2 or 3 inhalers each with 120 actuations.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

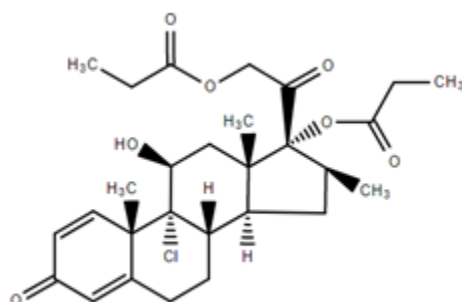
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

The canister contains a pressurised liquid. Do not puncture, expose to heat (temperatures higher than 50°C) or incinerate even when empty.

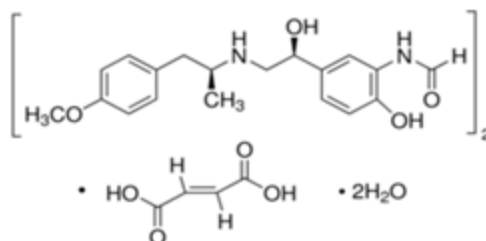
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

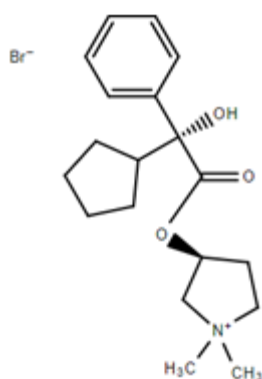
Beclometasone dipropionate



Formoterol fumarate dihydrate



Glycopyrronium bromide



CAS number

Beclometasone dipropionate: 5534-09-8

Formoterol fumarate dihydrate: 183814-30-4

Glycopyrronium bromide: 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

19 November 2025

Summary table of changes

Section changed	Summary of new information
10	Date of revision updated to reflect revised effective date for registration.