

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **TRIMBOW™**

Beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate dihydrate  
pressurized inhalation solution

For oral inhalation use

100 mcg beclomethasone dipropionate / 10 mcg glycopyrronium (as bromide) / 6 mcg formoterol  
fumarate dihydrate per metered actuation

Inhaled Corticosteroid (ICS) and Inhaled Bronchodilators (Long-Acting Muscarinic Antagonist (LAMA) and  
Long-Acting Beta2-Adrenergic Agonist (LABA)) Combination

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**RECENT MAJOR LABEL CHANGES**

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

TRIMBOW™ (beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate dihydrate) pressurized inhalation solution is a combination of an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta2-adrenergic agonist (LABA), indicated in adult patients who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA:

- for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
- to reduce exacerbations of COPD in patients with a history of exacerbations

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of TRIMBOW in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (≥ 65 years of age):** No dosage adjustment is required in patients 65 years of age and older.

### 2 CONTRAINDICATIONS

TRIMBOW is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

- Counselling by healthcare professionals on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e., chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.
- As with other inhaled drugs containing beta2-adrenergic agents, TRIMBOW should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA or LAMA, as an overdose may result.
- When beginning treatment with TRIMBOW, patients who have been taking rapid onset, short duration, inhaled beta2-agonists on a regular basis should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute respiratory symptoms while taking TRIMBOW.
- TRIMBOW should not be used to treat acute symptoms of COPD. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve acute symptoms such as shortness of breath and advised to have this available for use at all times.
- Patients should be made aware that for optimum benefit, TRIMBOW must be used regularly, even when asymptomatic.

## 4.2 Recommended Dose and Dosage Adjustment

The recommended and maximum dose of TRIMBOW is two inhalations twice daily, as two inhalations in the morning and two inhalations in the evening at the same time every day.

**Pediatrics (< 18 years of age):** TRIMBOW should not be used in patients under 18 years of age.

**Geriatrics (≥ 65 years of age):** No dosage adjustment is required in patients 65 years of age and older.

### Renal impairment

Glycopyrronium is primarily eliminated via renal metabolism, thus use in patients with severe (GFR <30 mL/min/1.73 m<sup>2</sup>) renal impairment or end-stage renal (GFR <15 mL/min/1.73 m<sup>2</sup>) disease requiring dialysis, especially if associated with significant body weight reduction, should be considered only if the expected benefit outweighs the potential risk and patients should be closely monitored (see 7 WARNINGS AND PRECAUTIONS, Renal and 10.3 Pharmacokinetics, Renal Insufficiency). No dose adjustment is required in patients with mild to moderate renal impairment.

### Hepatic impairment

Due to formoterol being primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment (classified as having Child-Pugh class C), and patients with hepatic disease should be closely monitored. The medicinal product should be used with caution in these patients (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Hepatic Insufficiency).

## 4.4 Administration

TRIMBOW is for oral inhalation only.

TRIMBOW should be administered as two inhalations twice daily, as in two inhalations in the morning and two inhalations in the evening at the same time every day. Patients should be advised to rinse their mouth with water (without swallowing) after inhaling the prescribed dose.

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 and carefully follow the instructions for use (see Patient Medication Information, Instructions for Use).

## 4.5 Missed Dose

If a dose is missed, the patient should be instructed to take the next dose as soon as they remember, unless it is almost time for the next dose, in which case the next dose should be taken at the correct time. The patient should be instructed not to double the dose.

## 5 OVERDOSE

An overdose of TRIMBOW may produce signs and symptoms due to the individual components' pharmacological actions (see 7 WARNINGS AND PRECAUTIONS).

An overdose of TRIMBOW may lead to exaggerated anticholinergic and/or β<sub>2</sub>-adrenergic signs and symptoms; the most frequent of which include, dry mouth, nausea, muscle spasm, tremor, headache, palpitations, systolic hypertension, tachycardia, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia, hyperglycemia, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), constipation, difficulties in voiding. Acute overdosage with

beclomethasone, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects may appear, such as suppression of the hypothalamic pituitary adrenal axis function.

In the event of drug overdose, discontinue TRIMBOW and initiate appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta receptor blocker may be considered, for treating beta2-adrenergic effects, but only under the supervision of a physician and with extreme caution bearing in mind that such medicine can produce bronchospasm.

Cardiac monitoring including electrocardiogram monitoring is recommended in cases of overdosage.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition                                                                                                                                              | Non-medicinal Ingredients                                                           |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Inhalation use          | Pressurized inhalation solution<br>100 mcg beclomethasone dipropionate /<br>10 mcg glycopyrronium (as bromide)/<br>6 mcg formoterol fumarate dihydrate<br>per metered actuation | Ethanol anhydrous,<br>hydrochloric acid (as<br>aqueous solution), and<br>norflurane |

TRIMBOW is colourless to yellowish liquid solution.

TRIMBOW is an inhalation solution, resulting in an aerosol of extrafine particles, which is contained in a sealed pressurized aluminium container with a metering valve. The pressurized container is inserted in a polypropylene inhaler, which incorporates a mouthpiece and a dose counter (60 actuations or 120 actuations per pressurized container) or a dose indicator (180 actuations per pressurized container) and is provided with a polypropylene mouthpiece cap.

Each TRIMBOW metered dose (the dose leaving the valve) contains 100 mcg of beclomethasone dipropionate, 10 mcg of glycopyrronium (as bromide) and 6 mcg of formoterol fumarate dihydrate.

The delivered dose per actuation (the dose leaving the mouthpiece) contains 87 mcg of beclomethasone dipropionate, 9 mcg of glycopyrronium (as bromide) and 5 mcg of formoterol fumarate dihydrate.

Pack sizes:

Single pack of 1 container with either 60, 120 or 180 actuations.

Multipack of 2 containers with 120 actuations each (total of 240 actuations).

Multipack of 3 containers with 120 actuations each (total of 360 actuations).

## 7 WARNINGS AND PRECAUTIONS

### General

TRIMBOW is not indicated for the treatment of asthma.

**Serious Asthma-Related Events – Hospitalizations, Intubations, Death:** Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death (see Salmeterol Multicenter Asthma Research Trial (SMART)). Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta2- adrenergic Agonist Combination Products).

Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

### Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta2-adrenergic Agonist Combination Products

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol with fluticasone propionate, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol with fluticasone propionate. No safety study was conducted with TRIMBOW. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A single, blinded, independent, joint adjudication committee determined whether events were asthma related. The 3 adult and adolescent trials were designed to rule out a 2.0-fold increase in relative risk for ICS/LABA compared with ICS. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone. These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

**Table 2 Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older**

|                                                | ICS/LABA<br>(n=17,537) <sup>a</sup> | ICS<br>(n=17,552) <sup>a</sup> | ICS/LABA vs. ICS<br>Hazard Ratio<br>(95% CI) <sup>b</sup> |
|------------------------------------------------|-------------------------------------|--------------------------------|-----------------------------------------------------------|
| Serious asthma-related event <sup>c</sup>      | 116                                 | 105                            | 1.10 (0.85, 1.44)                                         |
| Asthma-related death                           | 2                                   | 0                              |                                                           |
| Asthma-related intubation (endotracheal)       | 1                                   | 2                              |                                                           |
| Asthma-related hospitalization (≥24-hour stay) | 115                                 | 105                            |                                                           |

ICS = Inhaled Corticosteroid; LABA = Long-acting Beta2-adrenergic Agonist.

<sup>a</sup> Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

<sup>b</sup> Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

<sup>c</sup> Number of subjects with an event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Subjects may have had one or more events, but only the first event was counted for analysis. A single, blinded, independent, joint adjudication committee determined whether events were asthma related.

#### Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol versus 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

**Not for Acute Use:** TRIMBOW should not be used for the relief of acute symptoms of COPD (i.e., as rescue therapy for the treatment of acute episodes of bronchospasm). Patients should be prescribed a rapid onset, short duration inhaled bronchodilator (e.g., salbutamol) to relieve acute symptoms such as shortness of breath, and advised to have this available for use at all times.

When beginning treatment with TRIMBOW, patients who have been taking a rapid onset, short duration, inhaled bronchodilator on a regular basis should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief if they develop acute symptoms while taking TRIMBOW.

**Deterioration of disease:** TRIMBOW should not be initiated in patients with acutely deteriorating COPD which may be a life-threatening condition. The use of TRIMBOW in this setting has not been studied and is not considered appropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If TRIMBOW no longer controls symptoms of bronchoconstriction, the patient's inhaled, short-acting bronchodilator becomes less effective or the patient needs more inhalation of a short-acting bronchodilator than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the treatment regimen should be undertaken at once.

Exacerbations may occur during treatment with TRIMBOW. Patients should be advised to continue treatment and seek medical advice if symptoms remain uncontrolled or worsen after initiation of therapy with TRIMBOW.

Patients should not stop therapy with TRIMBOW without physician supervision since symptoms may recur after discontinuation.

**Excessive use and use with other LABA and LAMA products:** TRIMBOW should not be used more often or at higher doses than recommended.

TRIMBOW should not be administered concomitantly with other medicines containing a long-acting beta2-adrenergic agonist (e.g., salmeterol, formoterol fumarate, indacaterol, olodaterol), or a long-acting muscarinic antagonist (e.g., tiotropium, glycopyrronium, aclidinium, umeclidinium) for any reason, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

**Anticholinergic effects:** Consistent with its antimuscarinic activity, TRIMBOW should be used with caution in patients with narrow-angle glaucoma (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic), prostatic hyperplasia, or urinary retention (see 7 WARNINGS AND PRECAUTIONS, Renal). Additionally, due to the anticholinergic effect of glycopyrronium, the long-term

co-administration with other anticholinergic-containing medicinal products is not recommended (see 9.4 Drug-Drug Interactions, [Pharmacodynamic interactions](#)).

### Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias, e.g., atrial fibrillation and tachycardia, may be seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including TRIMBOW. In case such effects occur, treatment may need to be discontinued.

Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Cardiovascular effects such as tachycardia, arrhythmia, palpitations, myocardial ischemia, angina pectoris, hypertension or hypotension have been associated with use of beta-adrenergic agonists. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Like all products containing sympathomimetic agents, TRIMBOW should therefore be used with caution in patients with unstable or life-threatening cardiovascular disease, especially coronary insufficiency, cardiac arrhythmias (including tachyarrhythmias), or hypertension.

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, ischemic heart disease, congestive heart failure), occlusive vascular diseases (particularly arteriosclerosis), arterial hypertension and aneurysm.

**Electrocardiography:** As with other beta2-agonists, caution is recommended if TRIMBOW is administered to patients with a known history of QTc prolongation, risk factors for torsade de pointes (e.g., hypokalemia), or patients who are taking medications known to prolong the QTc interval (see 9.2 [Drug Interactions Overview](#); and 10.2 [Pharmacodynamics](#)).

**Hemodynamics:** Like other beta2-agonists, formoterol fumarate can produce clinically significant cardiovascular effects in some patients as measured by an increase in pulse rate, systolic or diastolic blood pressure, or cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia and extrasystoles (see 8 [ADVERSE REACTIONS](#) and 10 [CLINICAL PHARMACOLOGY](#)). If such effects occur, TRIMBOW may need to be discontinued.

If anesthesia with halogenated anesthetics is planned, it should be ensured that TRIMBOW is not administered for at least 12 hours before the start of anesthesia as there is a risk of cardiac arrhythmias (see 9.4 [Drug-Drug Interactions](#)).

Caution is also required when treating patients with thyrotoxicosis, diabetes mellitus, pheochromocytoma and untreated hypokalemia.

### Driving and Operating Machinery

There have been no studies investigating the effect of TRIMBOW on the ability to perform tasks that require judgment, motor or cognitive skills. Based on the pharmacological profile (see 10 [CLINICAL PHARMACOLOGY](#)), TRIMBOW is expected to have no or negligible influence on the ability to drive and use machines. The occurrence of headache or blurred vision may influence the ability to drive or to use machinery.

## Ear/Nose/Throat

Localized infections of the mouth and pharynx with *Candida albicans*, which are associated with the use of inhaled glucocorticosteroids, have occurred in patients treated with TRIMBOW during clinical studies. Patients should therefore be advised to rinse their mouth with water (without swallowing) after inhalation of TRIMBOW to reduce the risk of oropharyngeal candidiasis.

When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with TRIMBOW continues. However, at times, therapy with TRIMBOW may need to be interrupted for the treatment of severe infections (see 9.4 Drug-Drug Interactions).

## Endocrine and Metabolism

**Hyperglycemia:** 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.

**Hypokalemia:** Potentially serious hypokalemia may result from beta2-agonist therapy. This has the potential to produce adverse cardiovascular effects. Particular caution is advised in patients with severe COPD as this effect may be potentiated by hypoxia. Hypokalemia may also be potentiated by concomitant treatment with other medicinal products which can induce hypokalemia, such as xanthine derivatives, steroids and diuretics (see 9.4 Drug-Drug Interactions, Pharmacodynamic interactions - Related to formoterol).

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

**Systemic corticosteroid effects:** Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. 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, cataracts, glaucoma, central serous chorioretinopathy 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 and in patients with fungal and viral infections in the airways.

**Hypercorticism and Adrenal Suppression:** Inhaled ICS can be absorbed into the circulation and can be systemically active (see 10.2 Pharmacodynamics). Exceeding the recommended dosage or co-administration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction (see 9.4 Drug-Drug Interactions).

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. In light of the possibility of systemic absorption of inhaled corticosteroids, patients treated with TRIMBOW should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response. If such effects occur, appropriate therapy should be considered.

**Systemic Steroid Replacement by Inhaled Steroid:** Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although TRIMBOW may control COPD symptoms during these episodes, in recommended doses it supplies less than normal physiological amount of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe COPD exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or severe COPD exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRIMBOW. Lung function (mean forced expiratory volume in 1 second [FEV<sub>1</sub>]), beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to TRIMBOW may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression), despite maintenance or even improvement of respiratory function.

**Reduction in Bone Mineral Density:** Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. If significant reductions in BMD are seen and TRIMBOW is still considered medically important for that patient's COPD therapy, use of medication to treat or prevent osteoporosis should be strongly considered.

**Co-existing Conditions:** TRIMBOW, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the rapid onset, short-duration, beta2-adrenoceptor agonist salbutamol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

## Hematologic

**Eosinophilic Conditions:** In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Physicians should be alerted to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between inhaled corticosteroids and these underlying conditions has not been established.

## Hepatic/Biliary/Pancreatic

Due to formoterol being primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment (classified as having Child-Pugh class C), and patients with hepatic disease. TRIMBOW should only be used in patients if the expected benefit outweighs the potential risk (see 10.3 Pharmacokinetics, Hepatic Insufficiency). These patients should be monitored for potential adverse reactions.

## Immune

**Hypersensitivity Reactions:** Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of TRIMBOW. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, discontinue TRIMBOW. The patient should NOT be re-challenged with TRIMBOW if this is identified as the cause of the hypersensitivity reaction (see 2 CONTRAINDICATIONS).

**Infections:** Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients using corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

It is important that even mild chest infections be treated immediately since COPD patients may be more susceptible to damaging lung infections than healthy individuals. Patients should be instructed to contact their physician as soon as possible if they suspect an infection.

Physicians should recommend that patients receive an annual influenza vaccination.

As with all medications containing a corticosteroid, TRIMBOW should be administered with caution, and only if necessary, in patients with active or quiescent tuberculosis infections of the respiratory tract; chronic or untreated infections such as systemic fungal, bacterial, viral, or parasitic; or ocular herpes simplex.

## Monitoring and Laboratory Tests

Potentially serious hypokalemia has been observed with other beta-agonist therapies, which may increase susceptibility to cardiac arrhythmias. It is therefore recommended that serum potassium levels be monitored in patients predisposed to low levels of serum potassium.

For patients at risk, monitoring of bone and ocular effects (cataract and glaucoma) should also be considered in patients receiving maintenance therapy with TRIMBOW.

Due to the hyperglycemic effect observed with other beta-agonists, additional blood glucose monitoring is recommended in diabetic patients.

Patients with hepatic impairment should be monitored for corticosteroid effects due to potentially increased systemic exposure of beclomethasone dipropionate.

### **Ophthalmologic**

Glaucoma and increased intraocular pressure have been reported in patients following the long-term administration of inhaled corticosteroids or with use of inhaled anticholinergics. Cataracts have also been reported in patients following the long-term administration of inhaled corticosteroids.

Long-term administration of inhaled corticosteroids may result in central serous chorioretinopathy (CSCR).

TRIMBOW, like other antimuscarinic-containing products, should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare professional immediately if any of these signs or symptoms develops.

Close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, narrow- or open-angle glaucoma, cataracts, and/or CSCR.

Additionally, due to the anticholinergic effect of glycopyrronium, the long-term co-administration with other anticholinergic-containing medicinal products is not recommended (see 9.4 Drug-Drug Interactions, Pharmacodynamic interactions).

### **Renal**

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 10.3 Pharmacokinetics, Renal Insufficiency). These patients should be monitored for potential adverse reactions.

TRIMBOW, like other antimuscarinic-containing products, should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a healthcare professional immediately if any of these signs or symptoms develops.

### **Reproductive Health: Female and Male Potential**

- **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 beclomethasone dipropionate, glycopyrronium bromide and formoterol fumarate in combination (100/25/6 mcg ratio) at oral doses  $\geq 2$  mg/kg/day. This is attributable to the beclomethasone 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 (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

## Respiratory

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

**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 across all studies. 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 smokers, patients with a history of prior pneumonia, older age, low body mass index (BMI) and patients with severe COPD. These factors should be considered when TRIMBOW is prescribed, and treatment re-evaluated if pneumonia occurs.

### Use with a spacer

Single dose pharmacokinetic data (see 10.3 [Pharmacokinetics](#)) 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 beclomethasone-17-monopropionate (BDP main active metabolite), by 15% for  $C_{max}$  and 21% for  $AUC_{0-30min}$ , formoterol by 58% for  $C_{max}$  and 53% for  $AUC_{0-30min}$  and glycopyrronium by 60% for both  $C_{max}$  and  $AUC_{0-30min}$ . The total exposure ( $AUC_{0-t}$ ) was increased by 45% for glycopyrronium while it was decreased for beclomethasone-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. Results of long-term clinical studies where the use of the AeroChamber Plus® spacer was permitted do not suggest additional safety concerns.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

There are no or limited amount of data from the use of TRIMBOW in pregnant women.

Studies in rats with beclomethasone dipropionate, glycopyrronium bromide and formoterol fumarate in combination (100/25/6 mcg ratio; given orally) showed embryofetal and pup loss, dystocia, decreased fetal/pup weight, increased fetal visceral variations and impaired fetal ossification (see 16 NON-CLINICAL TOXICOLOGY, [Reproductive and Developmental Toxicology](#)). These findings are principally attributable to beclomethasone 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 foetus. Infants and neonates born to mothers receiving substantial doses should be observed for adrenal suppression.

There are no adequate and well-controlled human studies that have investigated the effects of TRIMBOW during labour and delivery. Because beta-agonists may potentially interfere with uterine contractility, TRIMBOW should be used during labour only if the potential benefit justifies the potential risk.

### 7.1.2 Breast-feeding

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 beclomethasone dipropionate and its metabolites are also excreted in human milk.

It is unknown whether glycopyrronium or formoterol (including their metabolites) are excreted in human 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 woman.

### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** TRIMBOW is not indicated in the pediatric population as the safety and efficacy of TRIMBOW has not been evaluated in patients less than 18 years of age.

### 7.1.4 Geriatrics

**Geriatrics (≥ 65 years of age):** No dose adjustment is required in elderly patients.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The overall safety profile of TRIMBOW was generally consistent with the known pharmacologic class effects of ICSs, LAMAs and/or LABAs.

In the Phase III clinical trials conducted in patients with severe to very severe COPD, a total of 1451 patients were treated with TRIMBOW (BDP/GB/FF total daily dose 400/50/24 mcg) with a mean duration of exposure of 341 days and 342 days in the TRILOGY study and the TRIBUTE study, respectively. The most common treatment-related adverse events reported were oral candidiasis (1.2%), muscle spasms (0.6%), dry mouth (0.5%) and dysphonia (0.3%).

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The most frequently reported adverse events in the two pivotal Phase III, 52-week active-controlled studies in COPD (TRILOGY and TRIBUTE), regardless of causality, are presented in Table 3 and Table 4. The majority of the TEAEs reported were mild or moderate in intensity and resolved by the end of the study.

Study TRILOGY included 687 patients with COPD who received TRIMBOW (BDP/GB/FF) 100/10/6 mcg two inhalations twice daily, who were compared to 680 patients treated with an active comparator, a fixed combination of beclomethasone dipropionate and formoterol fumarate 100/6 mcg (BDP/FF) two inhalations twice daily, for up to 52 weeks.

**Table 3 Adverse Events with  $\geq 1\%$  Incidence with TRIMBOW in TRILOGY Clinical Trial**

| System Organ Class<br>Preferred Term                   | TRIMBOW<br>(BDP/GB/FF) pMDI<br>400/40/24 mcg <sup>a</sup><br>N=687 | Active Comparator<br>(BDP/FF) pMDI<br>400/24 mcg <sup>a</sup><br>N=680 |
|--------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------|
|                                                        | n (%)                                                              | n (%)                                                                  |
| <b>Cardiac disorders</b>                               |                                                                    |                                                                        |
| Atrial fibrillation                                    | 10 (1.5)                                                           | 9 (1.3)                                                                |
| Cardiac failure                                        | 7 (1.0)                                                            | 5 (0.7)                                                                |
| <b>Infections and infestations</b>                     |                                                                    |                                                                        |
| Nasopharyngitis                                        | 39 (5.7)                                                           | 38 (5.6)                                                               |
| Pneumonia <sup>b</sup>                                 | 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)                                                                |
| <b>Metabolism and nutrition disorders</b>              |                                                                    |                                                                        |
| Diabetes mellitus                                      | 7 (1.0)                                                            | 2 (0.3)                                                                |
| <b>Nervous system disorders</b>                        |                                                                    |                                                                        |
| Headache                                               | 12 (1.7)                                                           | 16 (2.4)                                                               |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                                                    |                                                                        |
| Dyspnoea                                               | 12 (1.7)                                                           | 13 (1.9)                                                               |
| <b>Musculoskeletal and connective tissue disorders</b> |                                                                    |                                                                        |
| Muscle spasms                                          | 8 (1.2)                                                            | 4 (0.6)                                                                |
| <b>Vascular disorders</b>                              |                                                                    |                                                                        |
| Hypertension                                           | 20 (2.9)                                                           | 16 (2.4)                                                               |

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

BDP/FF = beclomethasone dipropionate / formoterol fumarate

pMDI= pressurized metered dose inhaler

<sup>a</sup> Total daily dose

<sup>b</sup> Includes preferred terms of bronchopneumonia, pneumonia and pneumonia aspiration

Study TRIBUTE included 764 patients with COPD who received TRIMBOW 100/10/6 mcg, two inhalations, twice daily, who were compared to 768 patients treated with indacaterol/glycopyrronium bromide inhalation powder, hard capsule, once daily (110/50 mcg), for up to 52 weeks.

**Table 4 Adverse Events with ≥ 1% Incidence with TRIMBOW in TRIBUTE Clinical Trial**

| System Organ Class<br>Preferred Term                   | TRIMBOW<br>(BDP/GB/FF) pMDI<br>400/40/24 mcg <sup>a</sup><br>N=764 | Active Comparator<br>(Indacaterol/GB) DPI<br>110/50 mcg <sup>a</sup><br>N=768 |
|--------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------|
|                                                        | n (%)                                                              | n (%)                                                                         |
| <b>Cardiac disorders</b>                               |                                                                    |                                                                               |
| Cardiac failure                                        | 9 (1.2)                                                            | 7 (0.9)                                                                       |
| <b>Gastrointestinal disorders</b>                      |                                                                    |                                                                               |
| Abdominal distension                                   | 8 (1.0)                                                            | 5 (0.7)                                                                       |
| Diarrhoea                                              | 8 (1.0)                                                            | 8 (1.0)                                                                       |
| <b>Infections and infestations</b>                     |                                                                    |                                                                               |
| Nasopharyngitis                                        | 43 (5.6)                                                           | 37 (4.8)                                                                      |
| Pneumonia <sup>b</sup>                                 | 28 (3.7)                                                           | 27 (3.5)                                                                      |
| Oral candidiasis                                       | 13 (1.7)                                                           | 5 (0.7)                                                                       |
| Viral infection                                        | 12 (1.6)                                                           | 7 (0.9)                                                                       |
| Upper respiratory tract infection                      | 11 (1.4)                                                           | 11 (1.4)                                                                      |
| Respiratory tract infection viral                      | 9 (1.2)                                                            | 9 (1.2)                                                                       |
| Bronchitis                                             | 9 (1.2)                                                            | 6 (0.8)                                                                       |
| Influenza                                              | 8 (1.0)                                                            | 6 (0.8)                                                                       |
| <b>Musculoskeletal and connective tissue disorders</b> |                                                                    |                                                                               |
| Back pain                                              | 21 (2.7)                                                           | 23 (3.0)                                                                      |
| Arthralgia                                             | 10 (1.3)                                                           | 11 (1.4)                                                                      |
| <b>Nervous system disorders</b>                        |                                                                    |                                                                               |
| Headache                                               | 44 (5.8)                                                           | 35 (4.6)                                                                      |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                                                    |                                                                               |
| Dyspnoea                                               | 21 (2.7)                                                           | 21 (2.7)                                                                      |
| Cough                                                  | 13 (1.7)                                                           | 21 (2.7)                                                                      |
| <b>Vascular disorders</b>                              |                                                                    |                                                                               |
| Hypertension                                           | 15 (2.0)                                                           | 22 (2.9)                                                                      |

BDP/GB/FF = beclomethasone dipropionate / glycopyrronium (as bromide) / formoterol fumarate (TRIMBOW)  
pMDI = pressurized metered dose inhaler; DPI = Dry powder inhaler

<sup>a</sup> Total daily dose

<sup>b</sup> Includes preferred terms of bronchopneumonia, lobar pneumonia, interstitial lung disease, pneumonia, pneumonia bacterial, pneumonia streptococcal, pneumonia viral and pulmonary tuberculosis

### 8.3 Less Common Clinical Trial Adverse Reactions

In addition to adverse events reported in Table 3 and Table 4, treatment-related adverse events occurring at a rate of less than 1% in subjects with COPD receiving TRIMBOW in TRILOGY and TRIBUTE studies included:

**Gastrointestinal disorders:** dry mouth, stomatitis

**General disorders and administration site conditions:** asthenia

**Infections and infestations:** lower respiratory tract infection fungal, oral fungal infection, oropharyngeal candidiasis, pharyngitis

**Investigations:** electrocardiogram QT prolonged

**Metabolism and nutritional disorders:** decreased appetite, hypokalaemia

**Nervous system disorders:** tremor

**Psychiatric disorders:** anxiety

**Renal and urinary disorders:** dysuria

**Respiratory, thoracic and mediastinal disorders:** dry throat, dysphonia, pharyngeal erythema, pharyngeal inflammation, throat irritation

**Skin and subcutaneous tissue disorders:** pruritus

**Vascular disorders:** extravasation blood

## 8.5 Post-Market Adverse Reactions

The following additional relevant adverse reactions have been identified from post-approval use of TRIMBOW.

**Cardiac disorders:** angina pectoris, palpitations, tachycardia

**Eye disorders:** vision blurred

**Gastrointestinal disorders:** dyspepsia, dysphagia, nausea

**General disorders and administration site conditions:** fatigue, oedema peripheral

**Immune system disorders:** hypersensitivity (including erythema and lip oedema)

**Infections and infestations:** urinary tract infection

**Investigations:** blood pressure increased

**Musculoskeletal and connective tissue disorders:** musculoskeletal chest pain, myalgia, pain in extremity

**Nervous system disorders:** dizziness, dysgeusia, hypoaesthesia

**Psychiatric disorders:** insomnia, restlessness

**Renal and urinary disorders:** urinary retention

**Respiratory, thoracic and mediastinal disorders:** epistaxis, oropharyngeal pain, productive cough

**Skin and subcutaneous tissue disorders:** hyperhidrosis, rash, urticaria

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Information on TRIMBOW is based on the potential for interactions for each of its components.

Co-administration of TRIMBOW with other anticholinergic and/or long-acting beta2-adrenergic agonist containing medicinal products has not been studied and is not recommended.

### Drugs Known to Prolong the QTc Interval

As with other beta2-adrenergic agonists, TRIMBOW should be administered with caution to patients treated with quinidine, disopyramide, procainamide, antihistamines, monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

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 anesthesia with halogenated hydrocarbons.

### Sympathomimetic Agents

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of TRIMBOW (see 7 WARNINGS AND PRECAUTIONS).

### Treatments Leading to Hypokalemia

Beta-agonists have been associated with reductions in serum potassium levels. Concomitant treatment with xanthine derivatives, oral corticosteroids (e.g., prednisone), or non-potassium sparing diuretics may potentiate any hypokalemic effect of adrenergic agonists (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypokalemia and Hyperglycemia). Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

### Beta-Adrenergic Blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta2-adrenergic agonists, such as formoterol. Therefore, TRIMBOW should not be given together with beta-adrenergic blockers (including eye-drops) unless there are compelling reasons for their use. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

### Metabolic interactions

The possibility of systemic effects with concomitant use of beclomethasone with strong CYP3A inhibitors (i.e., ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such medicinal products.

Since glycopyrronium is eliminated mainly by the renal route, interaction could potentially occur with medicinal products affecting renal excretion mechanisms (see 10.3 Pharmacokinetics, Renal Insufficiency). 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 an increase in its total systemic exposure ( $AUC_{0-t}$ ) by 16% and a 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.

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

## 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 5 Established or Potential Drug-Drug Interactions**

| Drug Type                                                                                               | Source of Evidence | Effect                                                                                                                                                       | Clinical comment                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CYP3A inhibitors                                                                                        | T                  | May inhibit the metabolism of, and increase the systemic exposure to, beclomethasone and formoterol. Expected to increase the risk of systemic side effects. | Caution should be exercised during long-term treatment with a strong CYP3A inhibitor (i.e., itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products). |
| Sympathomimetic agents                                                                                  | T                  | Potential pharmacodynamics interaction (additive pharmacologic and adverse effects).                                                                         | Caution is recommended during concomitant use with long-acting sympathomimetic agents administered by any route.                                                                     |
| Drugs that prolong the QTc interval<br><br>Monoamine Oxidase Inhibitors and Tricyclic Antidepressants   | T                  | Potential pharmacodynamics interaction (prolongation of the QTc interval and increased risk of ventricular arrhythmias).                                     | Caution is recommended during concomitant therapy.                                                                                                                                   |
| Beta-adrenergic blockers (including ophthalmic agents)                                                  | T                  | Beta-adrenergic blockers may weaken or antagonize the effect of beta2-adrenergic agonists resulting in severe bronchospasm                                   | If concomitant therapy is required, cardio-selective beta-adrenergic blockers could be considered, although they should be administered with caution.                                |
| Anticholinergics                                                                                        | T                  | Potential for an additive interaction with concomitantly used anticholinergic medications.                                                                   | Avoid co-administration with other anticholinergic-containing drugs administered by any route.                                                                                       |
| Methylxanthine derivatives, oral corticosteroids (i.e., prednisone), or non-potassium sparing diuretics | T                  | Potential pharmacodynamic interaction (increased risk of hypokalemia)                                                                                        | Caution is recommended during concomitant therapy.                                                                                                                                   |

| Drug Type                                                  | Source of Evidence | Effect                                                                                        | Clinical comment                                                                                                                                                                      |
|------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cimetidine or other inhibitors of organic cation transport | CT                 | Increased total exposure (AUC) to glycopyrronium by 16% and decreased renal clearance by 20%. | Based on the magnitude of these changes, no clinically relevant drug interaction is expected when coadministered with cimetidine or other inhibitors of the organic cation transport. |

CT = Clinical Trial      T = Theoretical

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

TRIMBOW contains beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate (BDP/GB/FF) 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.

Beclomethasone 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.

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. Glycopyrronium is a high affinity muscarinic receptor antagonist with a greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor as it has been demonstrated.

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.

### 10.2 Pharmacodynamics

The primary pharmacodynamics of TRIMBOW in obstructive airway disease reflects the complementary mechanisms of action of the individual components.

### HPA Axis Effects

Effects on HPA-axis function are known to occur with systemic administration of corticosteroids and this systemic side effect has also been reported with inhaled and intranasal corticosteroid use associated with decreases in serum and urine cortisol levels.

### Class-Related Beta2-Adrenoceptor Systemic Effects

Class-related systemic effects that are known to occur with systemic administration of beta-agonists include hypokalemia, hyperglycaemia, and increases in blood pressure, heart rate and the QTc interval. Following inhaled administration these effects are limited by local topical administration in the lung, low clinical doses and first pass metabolism of the swallowed portion of the dose and also tended to diminish on repeat dosing.

### Cardiovascular effects

A thorough QT study was not performed with TRIMBOW. A Phase II, randomized double-blind, active-controlled, 3-arm parallel group cardiac safety study in patients with moderate to severe COPD assessed the effects of combining beclomethasone dipropionate / formoterol fumarate (400/24 mcg) with glycopyrronium bromide at two GB dose levels (50 mcg [therapeutic dose] and 100 mcg [supra-therapeutic dose]).

Using short terms time basis for calculation of heart rate, the time profile of heart rate and ECG parameters (including QTcF interval) were comparable in the three groups at both the first and the last day of study treatment. None of patients in any group had clinically significant prolongation of the QTcF interval and there were no relevant differences between treatments in changes in mean QTcF, from baseline on Day 1 and Day 14, as indicated by an upper limit of the 90% CI of adjusted mean differences always < 10 ms. There were no substantial differences between groups in incidence of 24-hour digital ECG Holter abnormal findings.

### 10.3 Pharmacokinetics

The systemic exposure to beclomethasone dipropionate (BDP), glycopyrronium (as bromide) (GB) and formoterol fumarate (FF) has been investigated in a pharmacokinetic study conducted in 65 healthy subjects. The study compared the PK of each active component following the administration of a single dose of TRIMBOW (4 inhalations of 100/10/6 mcg [total dose: 400 mcg BDP, 40 mcg GB, 24 mcg FF]) vs BDP/FF (4 inhalations of 100/6 mcg [total dose: 400 mcg BDP, 24 mcg FF]) and GB (4 inhalations of 10 mcg [total dose: 40 mcg GB]). The median time to reach  $C_{max}$  was 5 minutes for each of the active components. The median time to reach  $C_{max}$  for the active metabolite of BDP (beclomethasone-17-monopropionate) was 30 minutes. Table 6 below provides the PK parameters calculated for each active component after administration of a single dose of TRIMBOW (4 inhalations) to healthy subjects. This study also investigated the potential pharmacokinetic interaction between the BDP/FF and GB by comparing the pharmacokinetic data obtained after a single dose of TRIMBOW or after a single dose of BDP/FF or GB. No drug-drug interactions were observed between BDP/FF and GB.

**Table 6 Summary of TRIMBOW Pharmacokinetic Parameters in Healthy Subjects**

|                                         | <b>C<sub>max</sub></b><br><b>(pg/mL)</b> | <b>T<sub>max</sub> (h)</b> | <b>t<sub>½</sub> (h)</b> | <b>AUC<sub>0-∞</sub></b><br><b>(pg.h/mL)</b> |
|-----------------------------------------|------------------------------------------|----------------------------|--------------------------|----------------------------------------------|
| <b>Beclomethasone dipropionate</b>      | 1610 (747)                               | 0.08 (0.08; 0.10)          | --                       | 223 (104) <sup>a</sup>                       |
| <b>Beclomethasone-17-monopropionate</b> | 754 (278)                                | 0.50 (0.08; 4.00)          | 4.69 (1.05)              | 4585 (1103)                                  |
| <b>Glycopyrronium</b>                   | 25.5 (23.1)                              | 0.08 (0.08; 4.00)          | 22.2 (13.8) <sup>b</sup> | 142 (50.9) <sup>a</sup>                      |
| <b>Formoterol</b>                       | 31.6 (13.5)                              | 0.09 (0.08; 1.00)          | 8.19 (2.24)              | 126 (37.1)                                   |

<sup>a</sup> Value provided is for AUC<sub>0-t</sub>.<sup>b</sup> calculated for 9 out of 64 subjects

Single total dose (4 inhalations): 400 mcg BDP, 40 mcg GB, 24 mcg FF

Note: Values are arithmetic mean (SD), except for T<sub>max</sub>: median (min; max)**Absorption***Beclomethasone dipropionate:*

Inhaled beclomethasone dipropionate is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to beclomethasone-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 beclomethasone dipropionate is negligible; however, pre-systemic conversion to beclomethasone-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 beclomethasone dipropionate and beclomethasone-17-monopropionate respectively. Following intravenous dosing, the disposition of beclomethasone 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 beclomethasone dipropionate (20 L) and larger tissue distribution for its active metabolite (424 L). Plasma protein binding is moderately high.

*Glycopyrronium:*

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 10 to 40 mcg via pressurized metered dose inhaler in COPD patients, glycopyrronium showed linear pharmacokinetics with little systemic accumulation at steady state (median accumulation ratio 2.2-2.5).

*Formoterol:*

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.

## Distribution

*Beclomethasone dipropionate:*

See [Absorption](#).

*Glycopyrronium:*

The apparent volume of distribution ( $V_z$ ) of inhaled glycopyrronium was increased compared to intravenous infusion (6420 L versus 323 L), reflecting the slower elimination after inhalation.

*Formoterol:*

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 mcg of formoterol.

## Metabolism

*Beclomethasone dipropionate:*

See [Absorption](#).

*Glycopyrronium:*

The metabolic pattern of glycopyrronium *in vitro* (human, dog, rat, mouse, and rabbit 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.

*Formoterol:*

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.

## Elimination

*Beclomethasone dipropionate:*

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

*Glycopyrronium:*

The mean elimination half-life of glycopyrronium in healthy volunteers was approximately 6 hours after intravenous injection while after inhalation in COPD patients it ranged from 5 to 12 hours at steady state. After a glycopyrronium single intravenous 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).

#### *Formoterol:*

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12-96 mcg 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 mcg 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 mcg), 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 feces. The renal clearance of formoterol is 150 mL/min.

#### **Effect of a spacer**

The use of TRIMBOW with the AeroChamber Plus® spacer in COPD patients increased the lung delivery of beclomethasone-17-monopropionate, glycopyrronium and formoterol (maximum plasma concentration increased by 15%, 60% and 58% respectively). The total systemic exposure (as measured by AUC<sub>0-t</sub>) was slightly reduced for beclomethasone 17 monopropionate (by 37%) and glycopyrronium (by 45%), while it was increased for formoterol (by 24%). See 7 WARNINGS AND PRECAUTIONS, Use with a spacer.

#### **Special Populations and Conditions**

- **Age, Gender and Weight**

A population pharmacokinetic analysis was performed on data collected from 394 subjects with COPD for beclomethasone-17-monopropionate, 324 subjects for glycopyrronium and 387 subjects for formoterol. No significant effect of age and gender was observed on PK parameters of beclomethasone-17-monopropionate, glycopyrronium and formoterol, while body weight was found to influence pharmacokinetic parameters for all three components. More specifically, simulations performed with the PK models showed total systemic exposure increased by approximately 50% for subjects with low body weight (40 kg) and decreased by approximately 40% for high body weight (139 kg), compared to reference subjects (70 kg), for all three components.

- **Ethnic Origin**

In Asian subjects administered 4 inhalations (supra-therapeutic) of beclomethasone dipropionate, glycopyrronium bromide and formoterol fumarate (BDP/GB/FF) as a single dose (total dose 400/50/24 mcg), the systemic exposures (C<sub>max</sub> and AUC) were found to be comparable to Caucasian subjects administered the same single dose.

- **Hepatic Insufficiency**

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

The pharmacokinetics of glycopyrronium in patients with hepatic impairment has not been studied, however, as glycopyrronium is predominantly cleared by renal excretion, hepatic impairment is not thought to result in a clinically relevant increase of glycopyrronium systemic exposure.

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.

- **Renal Insufficiency**

Systemic exposure ( $AUC_{0-t}$ ) to beclomethasone dipropionate, to its metabolite beclomethasone-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<sup>2</sup>), as a consequence of a significant reduction of the amount excreted in urine (approximately 90% reduction of glycopyrronium renal clearance).

In addition, glomerular filtration rate (GFR, reflecting the level of renal impairment) was found to have an effect on glycopyrronium and formoterol bioavailability, with increased bioavailability observed when GFR decreased (10% change in GFR leads to around 5% and 4.25% change in bioavailability of glycopyrronium and formoterol, respectively).

Simulations performed with the pharmacokinetic models showed that when covariates had extreme values (i.e., body weight less than 40 kg and concomitant GFR below 27 mL/min/1.73 m<sup>2</sup>), exposure to beclomethasone-17-monopropionate, glycopyrronium and formoterol remains in approximately a 2.5-fold range compared to the exposure in a typical patient with median covariate values.

## 11 STORAGE, STABILITY AND DISPOSAL

**Prior to dispensing:** Store in a refrigerator (2 - 8°C). Do not freeze.

**After dispensing:**

*60 actuation pressurized container:* Store below 25°C for a maximum of 2 months.

*120 or 180 actuation pressurized container:* Store below 25°C for a maximum of 4 months.

Keep out of sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 12 SPECIAL HANDLING INSTRUCTIONS

Do not expose to temperatures higher than 50°C.

Do not use or store near heat or open flames.

Do not expose the canister directly to sunlight.

Do not pierce the pressurized container.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

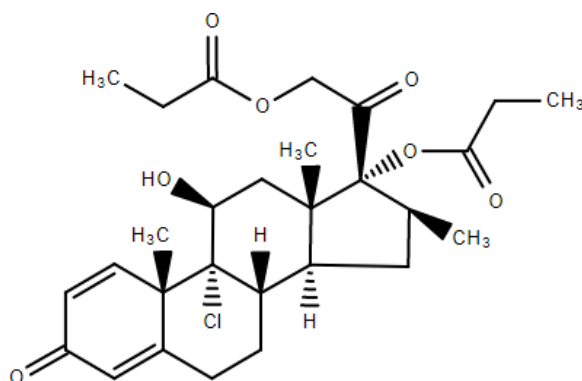
##### Beclomethasone dipropionate

Proper name: Beclomethasone dipropionate

Chemical name: [2-[(6S,9R,16R)-9-chloro-6-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-7,8,11,12,14,15,16,17-octahydro-6H-cyclopenta[a]phenanthren-17-yl]-2-oxoethyl] 2,2-dimethylpropanoate

Molecular formula and molecular mass:  $C_{28}H_{37}ClO_7$ ; 521.04 g/mol

Structural formula:



Physicochemical properties: A white or almost white, crystalline powder. Practically insoluble in water, freely soluble in acetone, and sparingly soluble in alcohol.

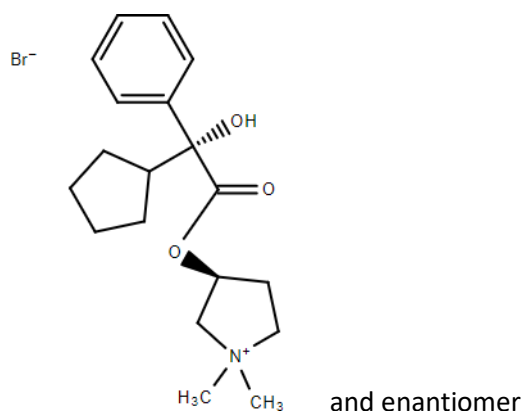
**Glycopyrronium bromide**

Proper name: Glycopyrronium bromide

Chemical name: Pyrrolidinium, 3-[(SR)-(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, [RS]-bromide

Molecular formula and molecular mass:  $C_{19}H_{28}BrNO_3$ ; 398.3 g/mol

Structural formula:



Physicochemical properties: White or almost white, crystalline powder. Freely soluble in water, soluble in ethanol, and very slightly soluble in methylene chloride.

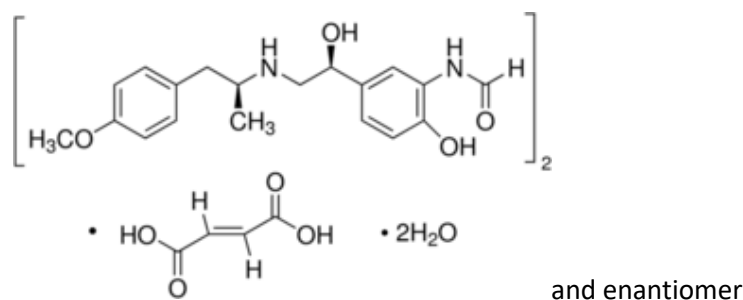
**Formoterol fumarate**

Proper name: Formoterol fumarate dihydrate

Chemical name: N-[2-Hydroxy-5-[1(RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (E)-butenedioate dehydrate

Molecular formula and molecular mass:  $C_{42}H_{52}N_4O_{12}$ ,  $2H_2O$ ; 840.91 g/mol

Structural formula:



Physicochemical properties: White to almost white or slightly yellow powder. Slightly soluble in water and ethanol, soluble in dimethylformamide, acetic acid, and methanol, and practically insoluble in isopropyl alcohol, dioxane and acetone.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

#### Chronic Obstructive Pulmonary Disease (COPD)

**Table 7 Summary of patient demographics for clinical trials in COPD**

| Study   | Study design                                                                                                                                                   | Dosage, route of administration and duration                                                                                                                                      | Study subjects (n)  | Mean age (Range)                    | Sex                                |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------|------------------------------------|
| TRILOGY | Phase III, randomised, double-blind, active controlled, 2-arm parallel group, multicentre, multinational<br><br>Active control: BDP/FF                         | TRIMBOW pMDI:<br>2 puffs bid (inhalation)<br>(TDD: 400/40/24 mcg BDP/GB/FF)<br><br>BDP/FF pMDI:<br>2 puffs bid (inhalation)<br>(TDD: 400/24 mcg BDP/FF)<br><br>52 weeks           | Total:<br>N = 1367  | Total:<br>63.6 years<br>(40 – 93)   | Total:<br>M (75.8%)<br>F (24.2%)   |
|         |                                                                                                                                                                |                                                                                                                                                                                   | TRIMBOW:<br>N = 687 | TRIMBOW:<br>63.3 years<br>(40 – 93) | TRIMBOW:<br>M (74.1%)<br>F (25.9%) |
|         |                                                                                                                                                                |                                                                                                                                                                                   | Control:<br>N = 680 | Control:<br>63.8 years<br>(40 – 86) | Control:<br>M (77.5%)<br>F (22.5%) |
| TRIBUTE | Phase IIIb, randomised, double-blind, double-dummy, active controlled, 2-arm parallel group, multicentre, multinational<br><br>Active controls: Indacaterol/GB | TRIMBOW pMDI:<br>2 puffs bid (inhalation)<br>(TDD: 400/40/24 mcg BDP/GB/FF)<br><br>Indacaterol/GB<br>1 capsule od<br>(TDD: 110/50 mcg [delivered dose 85/43 mcg])<br><br>52 weeks | Total:<br>N = 1532  | Total:<br>64.5 years<br>(41 – 87)   | Total:<br>M (71.8%)<br>F (28.2%)   |
|         |                                                                                                                                                                |                                                                                                                                                                                   | TRIMBOW:<br>N = 764 | TRIMBOW:<br>64.4 years<br>(42 – 87) | TRIMBOW:<br>M (71.7%)<br>F (28.3%) |
|         |                                                                                                                                                                |                                                                                                                                                                                   | Control:<br>N = 768 | Control:<br>64.5 years<br>(41 – 84) | Control:<br>M (71.9%)<br>F (28.1%) |

BDP= beclomethasone dipropionate; GB= glycopyrronium (as bromide); FF= formoterol fumarate; pMDI= pressurized metered dose inhaler; TDD= total daily dose; bid= twice daily; od= once daily

The Phase III clinical development programme in COPD was conducted with BDP/GB/FF (100/10/6 mcg - per metered actuation) and included two pivotal 52-week active-controlled studies.

The TRILOGY study compared TRIMBOW with a fixed combination of beclomethasone dipropionate and formoterol fumarate (BDP/FF) 100/6 mcg two inhalations twice daily (1368 randomised patients). The study was designed to demonstrate the superiority of TRIMBOW (BDP/GB/FF) pMDI versus BDP/FF pMDI in terms of lung function and dyspnea in patients with severe to very severe COPD. Co-primary endpoints were change from baseline in pre-dose and 2-hour post-dose morning FEV<sub>1</sub> and transition dyspnea index (TDI) focal score at Week 26. In addition to others, key secondary endpoints included: change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score and domain scores at all clinic visits, SGRQ response (change from baseline in total score  $\leq$  -4) at Week 26 and Week 52, use of rescue medication, moderate and severe COPD exacerbation rate over 52 weeks of treatment, and time to first moderate or severe COPD exacerbation.

The TRIBUTE study was a 52-week active-controlled study comparing TRIMBOW with a fixed combination of indacaterol/glycopyrronium bromide 110/50 mcg inhalation powder, hard capsule, one inhalation once daily (1532 randomised patients). The study was designed to demonstrate the

superiority of TRIMBOW pMDI versus indacaterol/GB in terms of moderate and severe COPD exacerbation rate over a 52-week treatment period in severe and very severe COPD patients. The primary endpoint was the number of moderate and severe COPD exacerbations over 52 weeks of treatment.

Selected key secondary endpoints included: time to first moderate or severe COPD exacerbation, number of severe COPD exacerbations over 52 weeks of treatment, change from baseline in the SGRQ total score and domain scores at all clinic visits and over the treatment period, SGRQ response (change from baseline in total score  $\leq -4$ ) at Week 26 and Week 52, use of rescue medication and change from baseline in CAT (COPD Assessment Test) score at the end of treatment.

Both studies were conducted in patients with a clinical diagnosis of COPD with severe to very severe airflow limitation ( $FEV_1$  less than 50% predicted), with symptoms assessed as a CAT score of 10 or above, and with at least one COPD exacerbation in the previous year. The two studies included approximately 20% of patients who used the AeroChamber Plus® spacer.

## Study Results

### TRILOGY Study

TRIMBOW (BDP/GB/FF) 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 8 and Figure 1).

TRIMBOW showed a numerical improvement compared with BDP/FF at Week 26 for dyspnea severity measured by the TDI focal score (co-primary endpoint) but did not demonstrate statistically significant improvement.

The lung function TDI outcomes at Week 52 were consistent with the results observed at Week 26.

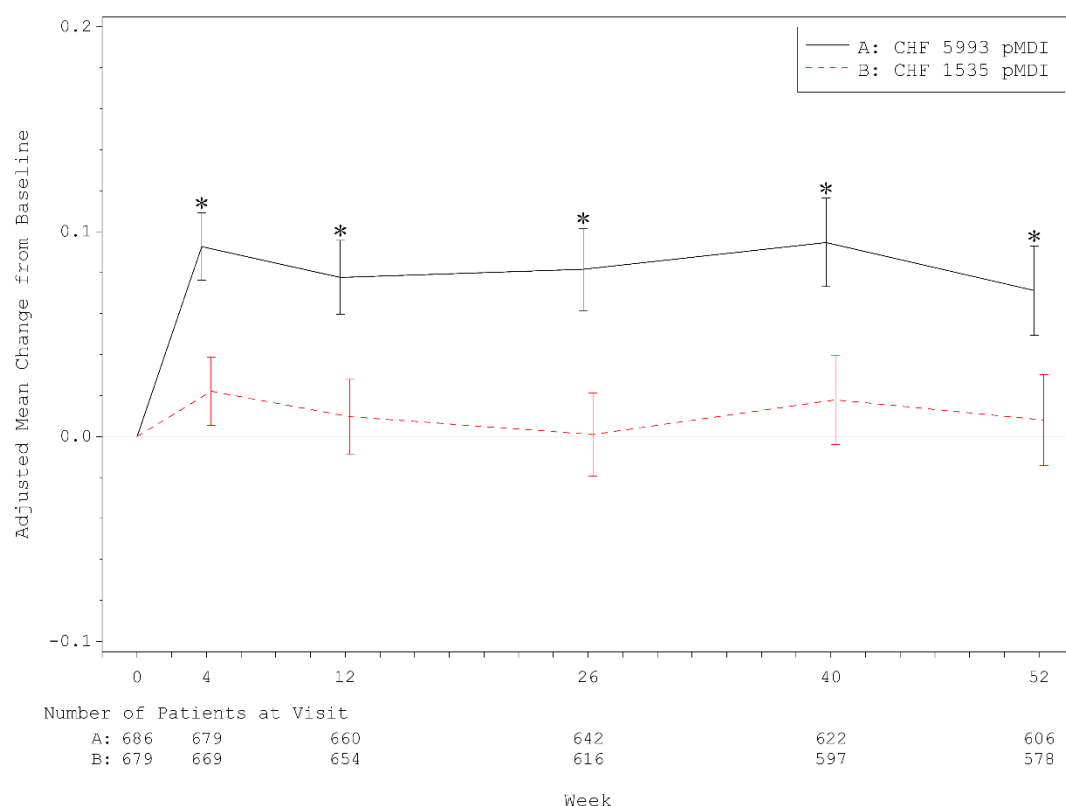
**Table 8 Primary Efficacy Endpoints, Intent-to-Treat (ITT) Population (TRILOGY Study)**

|                                                                                    | TRIMBOW<br>(BDP/GB/FF) pMDI<br>400/40/24 mcg <sup>a</sup><br>N = 687 | Active Comparator<br>(BDP/FF) pMDI<br>400/24 mcg <sup>a</sup><br>N = 680 |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|
| <b>Primary endpoints</b>                                                           |                                                                      |                                                                          |
| <b>Change from baseline in pre-dose morning FEV<sub>1</sub> (L) at Week 26 (L)</b> |                                                                      |                                                                          |
| 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                                                              |                                                                          |
| <b>Change from baseline in 2-hour post-dose FEV<sub>1</sub> (L) at Week 26 (L)</b> |                                                                      |                                                                          |
| 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                                                              |                                                                          |
| <b>TDI focal score at Week 26</b>                                                  |                                                                      |                                                                          |
| 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                                                                |                                                                          |

<sup>a</sup> Total daily dose; administered orally as two inhalations of TRIMBOW 100/10/6 mcg, BDP/FF 100/6 mcg, twice daily.

BDP= beclomethasone dipropionate; COPD= chronic obstructive pulmonary disease; FEV<sub>1</sub>= forced expiratory volume in 1 second; FF= formoterol fumarate; GB= glycopyrronium (as bromide); n= number of patients with available data; N= number of patients in the ITT population; pMDI= pressurized metered dose inhaler; TDI= transitional dyspnoea index.

**Figure 1 Adjusted Mean Change from Baseline in Pre-dose Morning FEV<sub>1</sub>, ITT Population (TRILOGY Study)**



CHF 5993 pMDI = BDP/GB/FF; CHF 1535 pMDI = BDP/FF.

Note: Bars represent 95% CI and the symbol \*, statistically significant difference between treatments ( $p < 0.05$ ).

### **TRIBUTE Study**

TRIMBOW (BDP/GB/FF) demonstrated a statistically significant reduction in the annual rate of moderate/severe exacerbations (i.e., requiring treatment with antibiotics or corticosteroids or hospitalization) compared with IND/GB (primary endpoint) (see Table 9). 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 but did not reach statistical significance.

Although not statistically significant, TRIMBOW improved average pre-dose FEV<sub>1</sub> over the 52-week treatment period compared to IND/GB by 22 mL ( $p = 0.018$ ).

**Table 9 Key efficacy endpoints, ITT population (TRIBUTE Study)**

|                                                          | <b>TRIMBOW<br/>(BDP/GB/FF) pMDI<br/>400/40/24 mcg <sup>a</sup><br/>N = 764</b> | <b>Active Comparator<br/>(Indacaterol/GB) DPI<br/>110/50 mcg <sup>b</sup><br/>N = 768</b> |
|----------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>Primary endpoint</b>                                  |                                                                                |                                                                                           |
| <b>Moderate/severe COPD exacerbation rate</b>            |                                                                                |                                                                                           |
| 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                                                                          |                                                                                           |
| % rate reduction                                         | 15.2%                                                                          |                                                                                           |

<sup>a</sup> Total daily dose; administered orally as two inhalations of TRIMBOW 100/10/6 mcg, twice daily.

<sup>b</sup> Total daily dose; administered orally as one inhalation of Indacaterol/GB 110/50 mcg, daily.

BDP= beclomethasone dipropionate; COPD= chronic obstructive pulmonary disease; FEV<sub>1</sub>= forced expiratory volume in 1 second; FF= formoterol fumarate; GB= glycopyrronium (as bromide); n= number of patients with available data; N= number of patients in the ITT population.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology:

#### Safety pharmacology

In an inhalation study in telemetered dogs, the cardiovascular system was a major target system for acute effects of TRIMBOW (increase in heart rate, decrease in blood pressure, ECG changes at higher doses), effects probably mainly related to the anti-muscarinic activity of glycopyrronium and the beta2-adrenergic activity of formoterol. There was no evidence for over-additive effects of the triple combination when compared with the single components.

#### Repeated dose toxicity

In repeated dose inhalation studies with TRIMBOW in rats and dogs of up to 13 weeks duration, the main observed alterations were related to effects on the immune system (probably due to systemic corticosteroid effects of beclomethasone dipropionate and its active metabolite beclomethasone-17-monopropionate), and on the cardiovascular system (probably related to the anti-muscarinic activity of glycopyrronium and the beta2-adrenergic activity of formoterol). The toxicological profile of the triple combination reflected that of the single active components without a relevant increase in toxicity and without unexpected findings.

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

*Beclomethasone dipropionate*

The potential carcinogenicity of beclomethasone 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.

*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 mcg/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.

*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 ( $\geq 20$  mg/kg in females and  $\geq 50$  mg/kg in males), leiomyomas and leiomyosarcomas in the female reproductive tract ( $\geq 2$  mg/kg/day) and adrenal subcapsular cell tumours ( $\geq 69$  mg/kg/day). In rats, treatment was associated with benign granulosa/theca cell tumours in the ovaries ( $\geq 0.5$  mg/kg/day) and mesovarian leiomyomas ( $\geq 15$  mg/kg/day). Smooth muscle tumours in the female reproductive tract and effects on the ovary have been reported in rats and mice treated with other beta2-adrenergic agonists and are likely to be secondary to prolonged stimulation of beta2-adrenoceptors in these tissues.

**Genotoxicity:** Genotoxicity of TRIMBOW has not been evaluated. However, individually, beclomethasone dipropionate, glycopyrronium bromide and formoterol fumarate 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).

**Reproductive and Developmental Toxicology:** Beclomethasone dipropionate/beclomethasone-17-monopropionate was considered responsible for reproductive toxicity effects in rats such as reduction of the conception rate, fertility index, early embryonic development parameters (implantation loss), delay in ossification and increased incidence of visceral variations; while tocolytic and anti-muscarinic effects, attributed to the anti-muscarinic activity of glycopyrronium and the beta2-adrenergic activity of formoterol, affected pregnant rats in the late phase of gestation and/or early phase of lactation, leading to loss of pups.

## Patient Medication Information

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **TRIMBOW™**

**beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate dihydrate pressurized inhalation solution**

This patient medication information is written for the person who will be taking **TRIMBOW**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TRIMBOW**, talk to a healthcare professional.

#### What **TRIMBOW** is used for:

**TRIMBOW** is used in adults who have not been adequately treated by certain combination inhaler medications:

- for the long-term treatment of chronic obstructive pulmonary disease (COPD; a lung disease that makes it hard to breathe), by managing airway blockage. This can include chronic bronchitis (inflammation of the lungs) and emphysema (damage to parts of the lung known as alveoli).
- to make breathing easier and help prevent worsening of COPD symptoms (“flare-ups”). You may experience “flare-ups” during which your symptoms become worse. If you have a history of experiencing “flare-ups”, **TRIMBOW** can help prevent them from developing in the first place.

**TRIMBOW** is not meant to treat asthma, or to provide immediate relief of an asthma attack. Use a fast acting “rescue” inhaler for any sudden asthma attacks. If you do not have a rescue inhaler, ask your healthcare professional to prescribe one for you.

#### How **TRIMBOW** works:

**TRIMBOW** contains 3 medicinal ingredients:

- beclomethasone dipropionate, an inhaled corticosteroid (ICS).
- glycopyrronium (as bromide), a long-acting muscarinic antagonist (LAMA).
- formoterol fumarate dihydrate, a long-acting beta2 agonist (LABA).

Beclomethasone dipropionate belongs to a group of medicines called corticosteroids. It reduces inflammation in the airways of your lungs, which can ease breathing problems, and help prevent “flare-ups” of your COPD.

Glycopyrronium and formoterol fumarate dihydrate belong to a group of medicines called long-acting bronchodilators. These two medicines work together to help open and relax the muscles of the airways. This allows more air to get in and out of the lungs. This makes it easier for people with COPD to breathe and helps prevent shortness of breath and wheezing.

**TRIMBOW** is not a cure for COPD, but it can help to control it. Therefore, it is important to continue to take it regularly, even if you feel fine.

**The ingredients in TRIMBOW are:**

Medicinal ingredients: beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate dihydrate.

Non-medicinal ingredients: ethanol anhydrous, hydrochloric acid (as aqueous solution), and norflurane.

**TRIMBOW comes in the following dosage form:**

Pressurized inhalation solution in a metered dose inhaler (for oral inhalation): 100 mcg beclomethasone dipropionate / 10 mcg glycopyrronium (as bromide) / 6 mcg formoterol fumarate dihydrate per metered actuation (also called puffs).

**Do not use TRIMBOW:**

- if you are allergic to beclomethasone dipropionate, glycopyrronium bromide, formoterol fumarate dihydrate or any of the other ingredients in TRIMBOW.
- to treat sudden severe symptoms of COPD (sudden shortness of breath or wheezing). **TRIMBOW is not a rescue inhaler and should not be used to give you fast relief from your COPD.** You must use a rescue inhaler during sudden COPD flare-ups. Keep this rescue medication with you at all times.
- to treat asthma.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRIMBOW. Talk about any health conditions or problems you may have, including if you:**

- are using a rescue inhaler on a regular basis.
- are a smoker. It is important to quit smoking if you use TRIMBOW, this will help decrease the symptoms of COPD and may increase your lifespan.
- have heart problems such as:
  - heart disease.
  - rapid or irregular heart beat or any problems with how your heart beats.
  - a condition called “QT prolongation”.
- have high blood pressure.
- have poor blood flow to the heart due to blockage or narrowing of the blood vessels.
- know that you have an abnormal bulge in the wall of a blood vessel (also known as an aneurysm).
- used to take 20 mg or more of prednisone per day.
- have prostate or bladder problems, or any problems passing urine.
- have problems with your thyroid gland.
- have diabetes.
- have a tumour of the adrenal gland (also known as a pheochromocytoma).
- have low levels of potassium in your blood.
- have or are at risk for decreased bone mineral content.
- are planning to have any surgery or dental procedures under anesthesia. Tell your healthcare professionals, including dentists, that you are taking TRIMBOW. They may ask you to stop using TRIMBOW at least 12 hours before your surgery or procedure.
- have kidney or liver problems.
- have ever had to stop taking another medication for your breathing problems because you were allergic to it or it caused problems.

- have been taking other corticosteroids by mouth or inhalation.
- have any allergies to food or medicines.
- have or ever had tuberculosis.
- have or have a history of lung infections such as pneumonia.
- have chronic or untreated infections such as:
  - bacterial infection
  - viral infection
  - fungal infection (yeast infection or thrush)
  - parasitic infection
  - herpes simplex infection of the eye
- are pregnant or trying to become pregnant. Your healthcare professional will consider the benefit to you and the risk to your unborn baby. Talk to your healthcare professional **right away** if you become pregnant while taking TRIMBOW.
- are breastfeeding or planning to breastfeed. You and your healthcare professional should decide if you should breastfeed or use TRIMBOW. You should not do both.
- have eye problems such as increased pressure in the eye, glaucoma, cataracts, blurry vision or other changes in vision.
- have ever had seizures.

**Other warnings you should know about:**

Do not stop taking TRIMBOW without talking to your healthcare professional first. If you stop treatment on your own, your symptoms may worsen. Talk to your healthcare professional **right away** if during your treatment with TRIMBOW:

- there is a change in your symptoms such as more coughing, wheezing, chest tightness or breathlessness;
- you find that you need to use your rescue inhaler more often than usual.

These could be warning signs that your condition may be getting worse.

**Alcohol content:** TRIMBOW contains a small amount of alcohol (ethanol) in each actuation. The amount in two puffs of this medicine is equivalent to less than 1 mL of wine or beer. The small amount of alcohol in this medicine will not have any noticeable effects.

**Paradoxical bronchospasm:** If you feel tightness of the chest, coughing, wheezing or breathlessness right after using TRIMBOW, you may have a serious condition called “paradoxical bronchospasm” (an unexpected closing of your airways). Stop using TRIMBOW and seek medical help **right away**.

**Eye problems:** TRIMBOW can cause eye disorders such as:

- Cataracts: clouding of the lens in the eye, blurry vision, eye pain;
- Glaucoma: an increased pressure in your eyes, eye pain, halos around lights or coloured images, red eyes. If left untreated, it may lead to permanent vision loss.
- Central serous chorioretinopathy (CSCR): blurry vision or other changes in vision.

If you have any changes in your vision, tell your healthcare professional **right away**. You may need regular eye exams.

**Chicken pox and measles:** You should avoid exposure to chicken pox and measles, and tell your healthcare professional if you are exposed. This is important if you are taking any cortisone-type medicine and your immune system is not working well (if you have difficulty in fighting an infection).

**Infections:** TRIMBOW may make you more susceptible to infections. If you experience an infection, it is important that you tell your healthcare professional **right away** even if it is mild.

**Eosinophilic granulomatosis with polyangiitis (EGPA):** Some people experience a flu-like illness called EGPA when taking an inhaled corticosteroid. Tell your healthcare professional if you have:

- a rash;
- pins and needles or numbness of your arms or legs;
- a severe sinus infection; and
- worsening lung or breathing problems.

**Driving and using machines:** TRIMBOW can cause headaches or blurry vision, which may affect your ability to drive and use machines. Use caution when driving and using machines until you know how TRIMBOW affects you.

**Monitoring:** During treatment with TRIMBOW, your healthcare professional may monitor:

- your bones and eyes;
- the effects of corticosteroid therapy on your body;
- your blood sugar levels, especially if you have diabetes;
- your blood potassium levels, especially if you already have low levels of potassium.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with TRIMBOW:**

- other medicines used to treat breathing problems, such as medicines containing tiotropium, ipratropium, aclidinium, umecclidinium, salmeterol, arformoterol, vilanterol, olodaterol, indacaterol, theophylline or aminophylline.
- medicines called “anticholinergics”.
- medicines used to treat bacterial infections, such as metronidazole or furazolidone.
- medicines used to treat fungal infections, such as ketoconazole or itraconazole.
- medicines used to treat HIV infection, such as ritonavir or cobicistat.
- medicines called beta-blockers, used to treat high blood pressure or other heart problems (e.g., atenolol, propranolol) or used to treat glaucoma (e.g., timolol).
- medicines used to treat abnormal heart rhythms, such as quinidine, disopyramide or procainamide.
- medicines used to treat allergies (also known as antihistamines).
- medicines used to treat depression, such as tricyclic antidepressants (e.g., phenelzine) or monoamine oxidase inhibitors (e.g., amitriptyline, imipramine).
- medicines used to treat symptoms of schizophrenia and other psychotic disorders, such as phenothiazines.
- medicines that lower the amount of potassium in your blood, such as some diuretics (also known as “water pills”).
- oral corticosteroids, used to suppress the immune system and treat inflammation (e.g., prednisone).

- certain anesthetics, used to prevent pain during surgery and other procedures.
- procarbazine, used to treat cancer.
- levodopa, used to treat Parkinson's disease.
- levothyroxine, used to treat an underactive thyroid gland.
- oxytocin, used to help start labour and control bleeding after delivery.
- disulfiram, used to treat alcohol dependence.
- alcohol.

#### **How to take TRIMBOW:**

- Read the Instructions for Use for complete information on how to use TRIMBOW. If you have any questions, talk to your healthcare professional.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- Take TRIMBOW exactly as your healthcare professional tells you to.
- Take everyday as prescribed, even if you have no symptoms of COPD.
- After you take your dose, always rinse your mouth with water and spit it out. Do not swallow.

#### **Usual dose:**

The recommended dose is 2 oral inhalations (puffs) twice daily in the morning and evening. They should be taken at the same time every day.

#### **Overdose:**

Signs of an overdose with TRIMBOW may include:

- dry mouth
- nausea or vomiting
- muscle spasms or shaking (tremors)
- headache
- fast heartbeat
- high blood pressure
- feeling sleepy
- increased pressure in the eye, which causes eye pain, vision changes or reddening of the eye
- increased blood sugar levels
- constipation
- being unable to pass urine

If you think you, or a person you are caring for, have taken too much TRIMBOW, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

#### **Missed dose:**

Do not take a double dose to make up for a forgotten dose. If you miss a dose, take it as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take more than 2 puffs twice a day.

**Possible side effects from using TRIMBOW:**

These are not all the possible side effects you may have when taking TRIMBOW. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with TRIMBOW may include:

- abnormal tastes
- cough
- diarrhea
- difficulty swallowing
- dry mouth
- excessive sweating
- feeling anxious
- feeling dizzy
- feeling sick (nausea)
- flu symptoms (fever, aches, chills)
- fungal or viral infection of the airways
- headache
- hoarse voice, irritated throat
- indigestion
- inflammation of the mouth and/or throat
- lack of energy or feeling restless
- muscle spasms, shaking (tremors)
- nose bleeds
- numbness
- pain in muscles, bones and joints
- pain or swelling of the hands, arms, legs or feet
- painful or difficult urination
- skin rash or itching
- stuffy or runny nose
- swollen abdomen
- trouble falling and/or staying asleep

**Serious side effects and what to do about them**

| Frequency/Side Effect/Symptom                                                                                                                                                                                              | Talk to your healthcare professional |              | Stop taking this drug and get immediate medical help |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|------------------------------------------------------|
|                                                                                                                                                                                                                            | Only if severe                       | In all cases |                                                      |
| Common                                                                                                                                                                                                                     |                                      |              |                                                      |
| <b>Pneumonia</b> (infection in the lungs): chest pain when you breathe or cough, confusion, cough which may produce phlegm, fatigue, fever, sweating and shaking chills, nausea, vomiting or diarrhea, shortness of breath |                                      | ✓            |                                                      |
| <b>Thrush</b> (yeast infection of the mouth or throat): thick white patches in the mouth, tongue or on the throat, sore throat                                                                                             |                                      | ✓            |                                                      |

| Frequency/Side Effect/Symptom                                                                                                                                                                                                                        | Talk to your healthcare professional |              | Stop taking this drug and get immediate medical help |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|------------------------------------------------------|
|                                                                                                                                                                                                                                                      | Only if severe                       | In all cases |                                                      |
| <b>Urinary tract infection</b> (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine |                                      | ✓            |                                                      |
| <b>Uncommon</b>                                                                                                                                                                                                                                      |                                      |              |                                                      |
| <b>Arrhythmia</b> (abnormal heart rhythms): rapid, slow or irregular heartbeat                                                                                                                                                                       |                                      | ✓            |                                                      |
| <b>Hyperglycemia</b> (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue                                                                                                                        |                                      | ✓            |                                                      |
| <b>Hypertension</b> (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, racing pulse or heart palpitations                                                                                           |                                      | ✓            |                                                      |
| <b>Hypokalemia</b> (low level of potassium in the blood): muscle weakness, muscle spasms, cramping, constipation, feeling of skipped heart beats or palpitations, fatigue, tingling or numbness                                                      |                                      | ✓            |                                                      |
| <b>Rare</b>                                                                                                                                                                                                                                          |                                      |              |                                                      |
| <b>Allergic reaction:</b> difficulty swallowing or breathing, wheezing, feeling weak or lightheaded, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue, or throat                                      |                                      |              | ✓                                                    |
| <b>Angina</b> (not enough oxygen to the heart muscle): discomfort in the shoulder, arm, back, throat, jaw or teeth, pain or pressure in the chest                                                                                                    |                                      | ✓            |                                                      |
| <b>Bronchospasm</b> (when there is a sudden narrowing of the airway): difficulty breathing with wheezing or coughing immediately after inhaling your medicine                                                                                        |                                      |              | ✓                                                    |
| <b>Urinary retention</b> (inability to pass urine or to empty the bladder): painful urination, pain or swelling in the lower abdomen                                                                                                                 |                                      | ✓            |                                                      |
| <b>Very rare</b>                                                                                                                                                                                                                                     |                                      |              |                                                      |
| <b>Cataracts:</b> clouding of the lens in the eye, blurry vision, dim vision and/or eye pain                                                                                                                                                         |                                      | ✓            |                                                      |
| <b>Decreased adrenal function:</b> tiredness, weakness, nausea and vomiting, low blood pressure                                                                                                                                                      | ✓                                    |              |                                                      |
| <b>Glaucoma:</b> increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, changes in vision, hazy or blurred vision, sudden sight loss                                                                          |                                      | ✓            |                                                      |

| Frequency/Side Effect/Symptom                                                                                                                                                                                                                                                                                                                                                                                   | Talk to your healthcare professional |              | Stop taking this drug and get immediate medical help |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                 | Only if severe                       | In all cases |                                                      |
| <b>Osteoporosis</b> (broken bone or weakening of the bones): in situations where healthy people would not normally break a bone you may have sudden pain in any location and especially in the wrist, spine, or hip                                                                                                                                                                                             |                                      | ✓            |                                                      |
| <b>Unknown</b>                                                                                                                                                                                                                                                                                                                                                                                                  |                                      |              |                                                      |
| <b>Depression</b> (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced sex drive and thoughts of death or suicide. If you have a history of depression, your depression may become worse. |                                      | ✓            |                                                      |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ([canada.ca/drug-device-reporting](http://canada.ca/drug-device-reporting)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### Storage:

Store below 25°C. Do not freeze.

**Warning:** The canister should not be broken, punctured or burnt, even when it seems empty. Do not use or store near heat or open flames. Do not expose the canister directly to sunlight. Do not expose to temperatures higher than 50°C.

**Use by date:** Do not use TRIMBOW after the expiry date on the label/carton. The expiry date refers to the last day of the month.

Once you receive your inhaler, it must be used:

- within 2 months for an inhaler that contains 60 actuations;
- within 4 months for an inhaler that contains 120 or 180 actuations; or
- by the expiry date, whichever comes first.

Dispose of your inhaler after the last dose, following local guidelines. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

Keep out of reach and sight of children.

**If you want more information about TRIMBOW:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website ([Drug Product Database: Access the database](#)); the distributor's website [www.methapharm.com](http://www.methapharm.com), or by calling 1-800-287-7686.

This leaflet was prepared by Chiesi Farmaceutici S.p.A.

Date of Authorization: 2025-04-28

## Instructions for Use

Pr **TRIMBOW™**

**beclomethasone dipropionate, glycopyrronium (as bromide) and formoterol fumarate dihydrate pressurized inhalation solution**

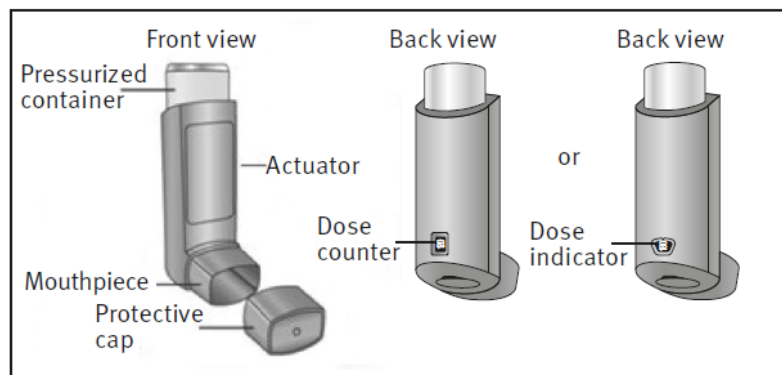
Read this Instructions for Use before you start using TRIMBOW and each time you get a new pack. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or treatment.

### Important Information:

- **For oral inhalation use only.**
- Use TRIMBOW exactly as your healthcare professional tells you to.
- If you have any questions about the use of your inhaler, ask your doctor or pharmacist.
- **Clean your inhaler once each week.** It is very important to keep the actuator clean so that the medicine will not build-up and block the spray through the mouthpiece. See Steps 1 through 5 under “How to clean your TRIMBOW inhaler”.

### Parts of your TRIMBOW inhaler (see Figure 1):

- TRIMBOW comes as a canister that fits into an actuator with a dose counter or indicator.
  - **Do not** use the TRIMBOW actuator with a canister of medicine from any other inhaler.
  - **Do not** use the TRIMBOW canister with an actuator from any other inhaler.



**Figure 1**

- TRIMBOW is available in three container sizes:
  - A container providing 60 puffs
  - A container providing 120 puffs
  - A container providing 180 puffs.

- There is a dose counter or indicator located on the back of the actuator (see **Figure 1**). The display window of the dose counter or indicator will show you how many puffs of medicine you have left. A puff of medicine is released each time you press the top of the canister.
  - **If you have been prescribed a container providing 60 puffs or 120 puffs:** Each time a puff of medicine is released, the dose counter will count down by one.
  - **If you have been prescribed a container providing 180 puffs:** Each time a puff of medicine is released, the dose indicator rotates by a small amount. The number of puffs remaining is displayed in intervals of 20 with the use of a pointer. For example, the pointer will be pointing between 160 and 180 after you take 10 puffs. This means that there are 170 puffs of medicine left in the canister.
- Take care not to drop the inhaler as this may cause the dose counter or dose indicator to count down.

### Priming your TRIMBOW inhaler:

#### Before you use TRIMBOW for the first time:

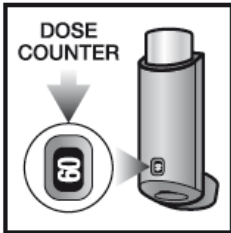
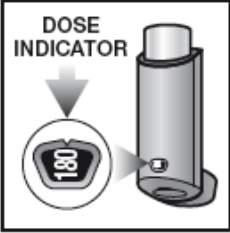
- **you must prime the inhaler so that you get the right amount of medicine when you use it.**
- depending on the container size prescribed to you (60 puffs, 120 puffs or 180 puffs), check that the dose counter reads 61 or 121, or that the dose indicator reads 180 respectively.

**Step 1:** Remove the cap from the mouthpiece.

**Step 2:** Hold your inhaler upright with the mouthpiece at the bottom.

**Step 3:** Direct the mouthpiece away from yourself and firmly press the top of the canister until the canister stops moving in the actuator to release a puff of medicine from the mouthpiece.

**Step 4:** Check the dose counter or dose indicator. If you are testing your inhaler for the first time, the counter or indicator should read:

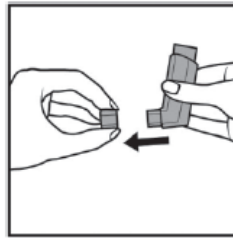
| 60                                                                                  | 120                                                                                 | 180                                                                                   |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| - when using the container providing 60 puffs                                       | - when using the container providing 120 puffs                                      | - when using the container providing 180 puffs                                        |
|  |  |  |

- An extra puff is provided for priming your inhaler when you use it for this first time. Do not skip priming.
- Re-prime your inhaler if it was not used for more than 14 days.

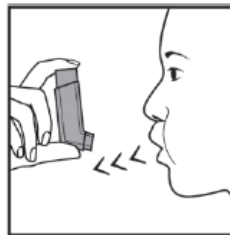
**Using your TRIMBOW inhaler:**

- Stand up or sit up when using TRIMBOW.
- IMPORTANT: **Do not** perform Steps 2 to 5 too quickly.

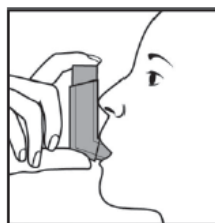
**Step 1:** Remove the cap from the mouthpiece and check that the mouthpiece is clean and free from dust and dirt (see **Figure A**).

**Figure A**

**Step 2:** Breathe out through your mouth, as slowly and fully as you comfortably can, to empty your lungs (see **Figure B**).

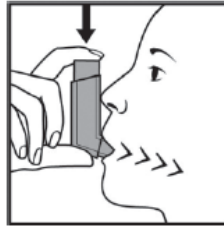
**Figure B**

**Step 3:** Hold the inhaler upright with the mouthpiece at the bottom and place the mouthpiece between your teeth without biting it. Close your lips around the mouthpiece, keeping your tongue flat below the mouthpiece (see **Figure C**).

**Figure C**

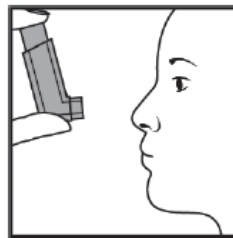
**Step 4:** Breathe in deeply and slowly through your mouth to fill your lungs with air (for about 4 - 5 seconds). Just after you start breathing in, press down firmly on the top of the canister until it stops moving in the actuator and a puff of medicine has been released (see **Figure D**). Then stop pressing the

canister.



**Figure D**

**Step 5:** Hold your breath for as long as you comfortably can (**see Figure E**). When you have finished holding your breath, remove the inhaler from your mouth and breathe out slowly. Do not breathe out into the inhaler.



**Figure E**

**Step 6:** Check that the dose counter has moved down by one (for the 60- or 120-puff inhaler) or that the dose indicator has rotated by a small amount (for the 180-puff inhaler).

For your second puff of TRIMBOW, keep the inhaler in the upright position for about half a minute, then **repeat Steps 2 to 6**.

If you see “mist” coming from the top of the inhaler or the sides of your mouth, this means that TRIMBOW did not get into your lungs as it should. Take another puff, following the instructions starting again from Step 2.

If you have a weak grip, it may be easier to hold the inhaler with both hands: hold the upper part of the inhaler with both index fingers and its lower part with both thumbs.

If you find it difficult to use the inhaler while starting to breathe in, you may use the AeroChamber Plus® spacer device. Ask your doctor or pharmacist about this device.

It is important that you read the package leaflet which is supplied with your AeroChamber Plus® spacer device. You should carefully follow the instructions on how to use the AeroChamber Plus® spacer device and how to clean it.

**Step 7:** Replace the cap over the mouthpiece right away after use.

**Step 8:** Rinse your mouth with water and spit it out. Do not swallow. This is to prevent fungal infections in the mouth and throat.

**How to clean your TRIMBOW inhaler:**

**Clean your inhaler once each week.** It is very important to keep your inhaler clean so that medicine will not build-up and block the spray through the mouthpiece.

**Step 1:**

- **Do not** remove the canister from the actuator. It should be kept in the actuator during cleaning.
- **Do not** use water or other liquids to clean your inhaler.

**Step 2:** Take the cap off the mouthpiece by pulling it away from your inhaler.

**Step 3:** Wipe inside and outside of the mouthpiece and the inhaler with a clean, dry cloth or tissue.

**Step 4:** Look into the mouthpiece to make sure any medicine build-up has been completely wiped away. If there is any build-up, repeat Step 3.

**Step 5:** Replace the cap on the mouthpiece.

**When to get a new inhaler:**

You should get a replacement when the dose counter or dose indicator shows the number 20. Stop using the inhaler when the counter or indicator shows 0. Any medicine left in the inhaler may not be enough to give you a full puff.

Date of Authorization: 2025-05-16