

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRIMBOW safely and effectively. See full prescribing information for TRIMBOW.

**TRIMBOW® (beclomethasone dipropionate, formoterol fumarate, and glycopyrrolate) inhalation aerosol, for oral inhalation use**  
Initial U.S. Approval: 2026

### INDICATIONS AND USAGE

TRIMBOW is a combination of beclomethasone dipropionate (BDP) (an inhaled corticosteroid [ICS]), formoterol fumarate (FF) (a long-acting beta<sub>2</sub>-adrenergic agonist [LABA]), and glycopyrrolate (G) (an anticholinergic) indicated for the maintenance treatment of asthma in adult patients aged 18 years and older. (1)

### Limitations of Use

Not indicated for relief of acute bronchospasm. (1)

### DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2.1)
- Prime TRIMBOW before first time use and re-prime if not used for 30 days or longer. (2.1)
- Recommended Dosage:** TRIMBOW 172 mcg/9.8 mcg/21.2 mcg (administered as 2 actuations of beclomethasone dipropionate 86 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) twice daily by oral inhalation or TRIMBOW 344 mcg/9.8 mcg/21.2 mcg (administered as 2 actuations of beclomethasone dipropionate 172 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) twice daily by oral inhalation. (2.2)

### DOSAGE FORMS AND STRENGTHS

Inhalation aerosol:

- 86 mcg/4.9 mcg/10.6 mcg (beclomethasone dipropionate 86 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) per actuation. (3)
- 172 mcg/4.9 mcg/10.6 mcg (beclomethasone dipropionate 172 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) per actuation. (3)

### CONTRAINDICATIONS

- Primary treatment of status asthmaticus or asthma requiring intensive measures. (4)
- Severe hypersensitivity to any of the ingredients. (4)

### WARNINGS AND PRECAUTIONS

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating asthma. Do not use to treat acute symptoms. (5.2)
- Avoid use in combination with additional therapy containing a LABA because of risk of overdose. (5.3)
- Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.5)

- Risk of impaired adrenal function when transferring from systemic corticosteroids. Wean patients slowly from systemic corticosteroids if transferring to TRIMBOW. (5.6)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue TRIMBOW slowly. (5.7)
- If paradoxical bronchospasm occurs, discontinue TRIMBOW and institute alternative therapy. (5.8)
- Use with caution in patients with cardiovascular disorders because of beta-adrenergic stimulation. (5.10)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.11)
- Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a healthcare provider immediately if symptoms occur. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRIMBOW long term. (5.12)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.13)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.14)
- Be alert to hypokalemia and hyperglycemia. (5.15)

### ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 1%) are bronchitis, hypertension, back pain, blood pressure increased, dysphonia, upper respiratory tract infection, influenza, anemia, muscle spasms, laryngitis, oropharyngeal pain, and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Chiesi USA, Inc. at 1-888-661-9260 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Other adrenergic drugs may potentiate effect: Use with caution. (7.1)
- Diuretics, xanthine derivatives or steroids may potentiate hypokalemia or ECG changes. Use with caution. (7.2)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol fumarate on cardiovascular system. (7.3)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.4)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of TRIMBOW with other anticholinergic-containing drugs. (7.6)

### USE IN SPECIFIC POPULATIONS

- Hepatic impairment: formoterol fumarate systemic exposure may increase in patients with severe hepatic impairment. Monitor for systemic beta-agonists effects. (8.6, 12.3)
- Renal impairment: In patients with severe renal impairment, use should be considered only if the potential benefit of the treatment outweighs the risk (8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA approved-patient labeling.

Revised: 05/2026

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

TRIMBOW is indicated for the maintenance treatment of asthma in adult patients aged 18 years and older.

#### Limitations of Use

TRIMBOW is NOT indicated for relief of acute bronchospasm [see *Warnings and Precautions (5.2)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Preparation and Administration Information

- Administer TRIMBOW by oral inhalation.
- After inhalation, rinse the mouth with water without swallowing it to help reduce the risk of oropharyngeal candidiasis [see *Warnings and Precautions (5.4)*].

#### Priming Before Use

- Prime TRIMBOW by actuating 2 times prior to using the first dose from a new canister.
- Re-prime if the inhaler has not been used for 30 days or longer.

#### Dose Counter

TRIMBOW has a dose counter attached to the canister. The counter starts at 122 and counts down each time a spray is released. The correct amount of medication in each actuation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000 or if 2 months have passed since first use date, whichever comes first.

#### 2.2 Recommended Dosage

The recommended dosage of:

TRIMBOW is beclomethasone dipropionate 172 mcg, formoterol fumarate 9.8 mcg, and glycopyrrolate 21.2 mcg (administered as 2 actuations of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg [beclomethasone dipropionate 86 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg]) twice daily (in the morning and evening) by oral inhalation.

or

TRIMBOW is beclomethasone dipropionate 344 mcg, formoterol fumarate 9.8 mcg, and glycopyrrolate 21.2 mcg (administered as 2 actuations of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg [beclomethasone dipropionate 172 mcg, formoterol fumarate 4.9 mcg, glycopyrrolate 10.6 mcg]) twice daily (in the morning and evening) by oral inhalation

- The recommended starting dosage for TRIMBOW is based upon patients' asthma severity or level of control of asthma symptoms on current inhaled corticosteroids.
- For patients who do not respond adequately to a starting dose of TRIMBOW 172 mcg/9.8 mcg/21.2 mcg (2 actuations of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg [beclomethasone dipropionate 86 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg]) twice daily, additional asthma control may be provided by replacement with a dose of TRIMBOW 344 mcg/9.8 mcg/21.2 mcg (2 actuations of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg [beclomethasone dipropionate 344 mcg, formoterol fumarate 9.8 mcg, and glycopyrrolate 21.2 mcg]) twice daily. For patients who do not respond adequately to a dose of TRIMBOW 344 mcg/9.8 mcg/21.2 mcg twice daily, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.
- The maximum recommended dosage is TRIMBOW 344 mcg/9.8 mcg/21.2 mcg (2 actuations of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg [beclomethasone dipropionate 344 mcg, formoterol fumarate 9.8 mcg, and glycopyrrolate 21.2 mcg]) twice daily by oral inhalation.
- Do not take more than two oral inhalations twice daily.

### 3 DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: a pressurized metered dose inhaler that delivers a combination of

- 86 mcg/4.9 mcg/10.6 mcg (beclomethasone dipropionate 86 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) per actuation. Inhaler supplied with a grey plastic actuator, dose counter, grey mouthpiece and red cap.
- 172 mcg/4.9 mcg/10.6 mcg (beclomethasone dipropionate 172 mcg, formoterol fumarate 4.9 mcg, and glycopyrrolate 10.6 mcg) per actuation. Inhaler supplied with grey plastic actuator, dose counter, grey mouthpiece and green cap.

### 4 CONTRAINDICATIONS

TRIMBOW is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required [see *Warnings and Precautions (5.2)*].
- Hypersensitivity to beclomethasone dipropionate, formoterol fumarate, glycopyrrolate or to any of the excipients [see *Warnings and Precautions (5.9)* and *Description (11)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of long-acting beta<sub>2</sub>-adrenergic agonists (LABA) as monotherapy [without inhaled corticosteroid (ICS)] for asthma is associated with an increased risk of asthma-related death. 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 (TRIMBOW is not indicated for pediatric 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 Beta<sub>2</sub>-adrenergic Agonists](#)).

## Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta<sub>2</sub>-adrenergic Agonists

Four 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 patients with asthma. Three trials included adult and adolescent patients aged 12 years and older: 1 trial compared budesonide/formoterol fumarate with budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol fumarate with mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma related. While these trials included pediatric patients aged 4 years and older, and the analysis below includes pediatric patients aged 12 years and older, TRIMBOW is not indicated for pediatric patients.

The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. 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 (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

**Table 1. Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older**

	ICS/LABA (n = 17,537) <sup>a</sup>	ICS (n = 17,552) <sup>a</sup>	ICS/LABA vs. ICS Hazard Ratio (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 Beta<sub>2</sub>-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 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 can have 1 or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric subjects aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) subjects randomized to ICS/LABA and 21/3,101 (0.7%) subjects randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

While the safety for pediatric patients is provided, TRIMBOW is not indicated for use in pediatric patients aged 17 years and younger.

#### 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 vs. 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.

### **5.2 Deterioration of Disease and Acute Episodes**

TRIMBOW should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. TRIMBOW has not been studied in subjects with acutely deteriorating asthma. The use of TRIMBOW in this setting is not appropriate.

Increasing use of inhaled, short-acting beta<sub>2</sub>-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the need for additional therapeutic options. Patients should not use more than 2 inhalations twice daily of TRIMBOW.

TRIMBOW should not be used for the relief of acute symptoms (i.e., as rescue therapy for the treatment of acute episodes of bronchospasm). TRIMBOW has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.

When beginning treatment with TRIMBOW, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing TRIMBOW, the healthcare provider should also prescribe an inhaled, short-acting beta<sub>2</sub>-agonist/corticosteroid combination or an inhaled, short-acting beta<sub>2</sub>-agonist and instruct the patient on how it should be used.

### **5.3 Avoid Excessive Use of TRIMBOW and Avoid Use with Other Long-acting Beta<sub>2</sub>-agonists**

TRIMBOW should not be used more often than recommended, at higher doses than recommended, or in conjunction with other therapies containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using TRIMBOW should not use another therapy containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol, vilanterol, olodaterol or indacaterol) for any reason.

### **5.4 Oropharyngeal Candidiasis**

TRIMBOW contains beclomethasone dipropionate, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in subjects treated with orally inhaled drug products containing beclomethasone dipropionate. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with TRIMBOW continues. In some cases, therapy with TRIMBOW may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of TRIMBOW to help reduce the risk of oropharyngeal candidiasis.

## 5.5 Immunosuppression and Risk of Infections

Patients who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The safety and effectiveness of TRIMBOW have not been established in pediatric patients and TRIMBOW is not indicated for use in this population. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. 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. (See the respective Prescribing Information for VZIG and IG.) If chickenpox develops, treatment with antiviral agents may be considered.

ICS should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

## 5.6 Transferring Patients from Systemic Corticosteroid Therapy

### HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (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 asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts 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 asthma exacerbation, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare practitioner 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 a severe asthma exacerbation.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to TRIMBOW. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with TRIMBOW. Lung function (forced expiratory volume in 1 second [FEV<sub>1</sub>] or morning peak expiratory flow [PEF]), beta-agonist use, and asthma 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.

### Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

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).

### Corticosteroid Withdrawal Symptoms

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.

## **5.7 Hypercorticism and Adrenal Suppression**

Inhaled beclomethasone dipropionate is absorbed into the circulation and can be systemically active. Effects of beclomethasone dipropionate on the HPA axis are not observed with the therapeutic doses of beclomethasone dipropionate in TRIMBOW. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A (CYP3A4 and CYP3A5) inhibitor may result in HPA dysfunction.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, 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.

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. If such effects occur, appropriate therapy should be initiated as needed.

## **5.8 Paradoxical Bronchospasm**

As with other inhaled therapies, TRIMBOW can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with TRIMBOW, it should be treated immediately with an inhaled, short-acting bronchodilator; TRIMBOW should be discontinued immediately; and alternative therapy should be instituted.

## **5.9 Hypersensitivity Reactions, including Anaphylaxis**

Hypersensitivity reactions have been reported after administration of beclomethasone dipropionate, formoterol fumarate or glycopyrrolate, the components of TRIMBOW. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips and face), urticaria or skin rash, TRIMBOW should be discontinued immediately, and alternative therapy instituted [see *Contraindications* (4)].

## **5.10 Cardiovascular Effects**

Formoterol fumarate, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles [see *Clinical Pharmacology* (12.2)]. If such effects occur, TRIMBOW may need to be discontinued.

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, although the clinical significance of these findings is unknown [see *Clinical Pharmacology* (12.2)]. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. TRIMBOW, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

### **5.11 Reduction in Bone Mineral Density**

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. 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.

### **5.12 Glaucoma and Cataracts, Worsening of Narrow-Angle Glaucoma**

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma following the long-term administration of ICS or with use of inhaled anticholinergics. TRIMBOW 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 provider immediately if any of these signs or symptoms develop. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use TRIMBOW long term.

### **5.13 Worsening of Urinary Retention**

TRIMBOW, like all therapies containing an anticholinergic, 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 provider immediately if any of these signs or symptoms develop.

### **5.14 Coexisting Conditions**

TRIMBOW, like all therapies 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 related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

### **5.15 Hypokalemia and Hyperglycemia**

Beta-adrenergic agonist therapies may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist therapies may produce transient hyperglycemia in some patients.

### **5.16 Effect on Growth**

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. TRIMBOW is not indicated for use in this population [see *Use in Specific Populations* (8.4)].

## **6 ADVERSE REACTIONS**

The following clinically significant adverse reactions are described elsewhere in labeling:

- Serious Asthma-Related Events – Hospitalizations, Intubations, Death [see *Warnings and Precautions* (5.1)]
- Oropharyngeal Candidiasis [see *Warnings and Precautions* (5.4)]
- Immunosuppression and Risk of Infections [see *Warnings and Precautions* (5.5)]

- Hypercorticism and Adrenal Suppression [see Warnings and Precautions (5.7)]
- Paradoxical Bronchospasm [see Warnings and Precautions (5.8)]
- Cardiovascular Effects [see Warnings and Precautions (5.10)]
- Reduction in Bone Mineral Density [see Warnings and Precautions (5.11)]
- Worsening of Narrow-Angle Glaucoma [see Warnings and Precautions (5.12)]
- Worsening of Urinary Retention [see Warnings and Precautions (5.13)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### 6.1 Clinical Trials Experience

The safety of TRIMBOW in asthma is based on the safety data from two randomized, double-blind, parallel-group, active-controlled trials of 52 weeks' duration (TRIMARAN and TRIGGER) that included 2,294 adult patients with asthma who received TRIMBOW or BDP/FF comparator [see Clinical Studies (14)]. The incidence of adverse reactions occurring in  $\geq 1\%$  of the patients treated with a dose of TRIMBOW 172 mcg/9.8 mcg/21.2 mcg or a dose of TRIMBOW 344 mcg/9.8 mcg/21.2 mcg, both doses at twice daily by oral inhalation, is shown in Table 2.

**Table 2. Adverse Reactions with TRIMBOW with  $\geq 1\%$  Incidence and Greater than Active Control in Adult Patients with Asthma in the TRIMARAN and TRIGGER 52-week Trials**

Adverse Reactions in TRIMARAN (n, %)	TRIMBOW 172 mcg/9.8 mcg/21.2 mcg twice daily (N = 576)	BDP/FF 172 mcg/9.8 mcg twice daily (N = 574)
Hypertension	16 (3)	9 (2)
Blood pressure increased	12 (2)	7 (1)
Dysphonia	11 (2)	3 (<1)
Upper respiratory tract infection	11 (2)	10 (2)
Influenza	9 (2)	7 (1)
Anemia	8 (1)	5 (1)
Adverse Reactions in TRIGGER (n, %)	TRIMBOW 344 mcg/9.8 mcg/21.2 mcg twice daily (N = 571)	BDP/FF 344 mcg/9.8 mcg twice daily (N = 573)
Bronchitis	18 (3)	18 (3)
Back pain	12 (2)	5 (1)
Dysphonia	11 (2)	9 (2)
Hypertension	10 (2)	7 (1)
Influenza	7 (1)	6 (1)
Muscle spasms	6 (1)	6 (1)
Laryngitis	6 (1)	3 (<1)
Oropharyngeal pain	6 (1)	3 (<1)
Sinusitis	6 (1)	3 (<1)

Abbreviations: BDP, beclomethasone dipropionate; FF, formoterol fumarate; N, number of patients

## 7 DRUG INTERACTIONS

### 7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol fumarate, a component of TRIMBOW, may be potentiated [see Warnings and Precautions (5.3)].

## 7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate the hypokalemic effect of beta<sub>2</sub>-adrenergic agonists such as formoterol fumarate, a component of TRIMBOW.

## 7.3 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and QTc Prolonging Drugs

Formoterol, as with other beta<sub>2</sub>-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, macrolides or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

## 7.4 Beta-adrenergic Receptor Blocking Agents

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta<sub>2</sub>-agonists, such as formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

## 7.5 Non-Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.

## 7.6 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of TRIMBOW with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions* (5.12, 5.13)].

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Risk Summary

There are no adequate and well-controlled studies with TRIMBOW or its individual components, beclomethasone dipropionate, formoterol fumarate, and glycopyrrolate in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes (See *Clinical Considerations*).

In animal reproduction studies, beclomethasone dipropionate (BDP) resulted in adverse developmental effects in mice and rabbits at subcutaneous doses equal to or greater than approximately 0.6 times the maximum recommended human daily inhalation dose (MRHDID) in adults (800 mcg/day) [see *Data*]. In rats exposed to beclomethasone dipropionate by inhalation, dose-related gross injury to the fetal adrenal glands was observed at doses greater than 140 times the MRHDID, but there was no evidence of external or skeletal malformations or embryoletality at inhalation doses of up to 350 times the MRHDID.

In animal reproduction studies, formoterol fumarate (FF) produced malformations that included umbilical hernia and brachygnathia (a skeletal malformation) in rats at oral doses 1,200 and 6,100 times the MRHDID in adults, respectively. In rabbits, formoterol fumarate produced subcapsular cysts on the liver at oral doses 49,000 times the MRHDID in adults. In rats exposed to formoterol fumarate by inhalation, no teratogenic effects were observed at 500 times the MRHDID in adults.

Glycopyrrolate (G) administered by the oral route in rats and rabbits did not cause structural abnormalities or affect fetal survival at exposures approximately 179 and 50 times MRHDID, respectively.

TRIMBOW administered by the oral route in rats caused reduction in fetal weights and increased incidence of visceral variations at doses 83 and 0.8 times the MRHDID and higher for BDP (metabolite- B17MP) and FF, respectively. TRIMBOW also caused decreased pup survival, increase in post-implantation loss and reduced mean litter size in rats at 1.9, 3.7, and 7.7 times the MRHDID (based on a mg/m<sup>2</sup>) for BDP, FF, and G, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### Clinical Considerations

#### *Disease-Associated Maternal and/or Embryofetal Risk:*

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored, and medication adjusted as necessary to maintain optimal control of asthma.

#### *Labor or Delivery:*

There are no well-controlled human trials that have investigated the effects of TRIMBOW on preterm labor or labor at term. TRIMBOW should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

Infants and neonates born to mothers receiving substantial doses should be observed for adrenal suppression. If treatment during pregnancy is necessary, the lowest effective dose should be used.

### Data

#### *Animal Data*

#### *Beclomethasone dipropionate (BDP)*

In an embryofetal development study in pregnant rats, beclomethasone dipropionate administration during organogenesis from gestation days 6 to 15 at inhaled doses 140 times the MRHDID in adults and higher (on a mg/m<sup>2</sup> basis at maternal doses of 11,500 and 28,300 mcg/kg/day) produced dose-dependent gross injury (characterized by red foci) of the adrenal glands in fetuses. There were no findings in the adrenal glands of rat fetuses at an inhaled dose that was 30 times the MRHDID in adults (on a mg/m<sup>2</sup> basis at a maternal dose of 2,400 mcg/kg/day). There was no evidence of external or skeletal malformations or embryoletality in rat at inhaled doses up to 350 times the MRHDID (on a mg/m<sup>2</sup> basis at maternal doses up to 28,300 mcg/kg/day).

In an embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 18 at subcutaneous doses equal to and greater than 0.6 times the MRHDID in adults (on a  $\text{mg}/\text{m}^2$  basis at maternal doses of 100  $\text{mcg}/\text{kg}/\text{day}$  and higher) produced adverse developmental effects (increased incidence of cleft palate). A no-effect dose in mice was not identified. In a second embryofetal development study in pregnant mice, beclomethasone dipropionate administration from gestation days 1 to 13 at subcutaneous doses equal to and greater than 2.0 times the MRHDID in adults (on a  $\text{mg}/\text{m}^2$  basis at a maternal dose of 300  $\text{mcg}/\text{kg}/\text{day}$ ) produced embryolethal effects (increased fetal resorptions) and decreased pup survival.

In an embryofetal development study in pregnant rabbits, beclomethasone dipropionate administration during organogenesis from gestation days 7 to 16 at subcutaneous doses equal to and greater than 0.6 times the MRHDID in adults (on a  $\text{mg}/\text{m}^2$  basis at maternal doses of 25  $\text{mcg}/\text{kg}/\text{day}$  and higher) produced external and skeletal malformations and embryolethal effects (increased fetal resorptions). There were no effects in fetuses of pregnant rabbits administered a subcutaneous dose 0.15 times the MRHDID in adults (on a  $\text{mg}/\text{m}^2$  basis at a maternal dose of 6  $\text{mcg}/\text{kg}/\text{day}$ ).

### Formoterol fumarate (FF)

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. When given to rats throughout organogenesis, oral doses equal to or greater than 80 times the MRHDID for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses of 200  $\text{mcg}/\text{kg}/\text{day}$  and above) delayed ossification of the fetus and doses equal to or greater than 2,400 times the MRHDID for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses of 6,000  $\text{mcg}/\text{kg}/\text{day}$  and above) decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses equal to or greater than 2,400 times the MRHDID for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses of 6,000  $\text{mcg}/\text{kg}/\text{day}$  and above) in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose equal to 80 times the MRHDID for adults (on a  $\text{mcg}/\text{m}^2$  basis for a maternal dose of 200  $\text{mcg}/\text{kg}/\text{day}$ ).

In another testing laboratory, formoterol fumarate was shown to be teratogenic in rats and rabbits. Umbilical hernia, a malformation, was observed in rat fetuses at oral doses equal to or greater than 1,200 times the MRHDID for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses of 3,000  $\text{mcg}/\text{kg}/\text{day}$  and above). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose equal to 6,100 times the MRHD for adults (on a  $\text{mcg}/\text{m}^2$  basis for a maternal dose of 15,000  $\text{mcg}/\text{kg}/\text{day}$ ). In another study in rats, no teratogenic effects were seen at inhalation doses up to 500 times the MRHD for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses up to 1,200  $\text{mcg}/\text{kg}/\text{day}$ ). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose equal to 49,000 times the MRHD for adults (on a  $\text{mcg}/\text{m}^2$  basis for a maternal dose of 60,000  $\text{mcg}/\text{kg}$ ). No teratogenic effects were observed at oral doses up to 3,000 times the MRHD for adults (on a  $\text{mcg}/\text{m}^2$  basis for maternal doses up to 3,500  $\text{mcg}/\text{kg}/\text{day}$ ).

### Glycopyrrolate (G)

In an embryo-fetal development study in pregnant rats, orally dosed during the period of organogenesis from gestation days 6 to 17, glycopyrrolate administration produced no structural abnormalities or effects on fetal survival at the highest tested dose that was 179 times the MRHDID. Maternal toxicity was characterized by significant reduction in maternal body weight observed at doses 26 times the MRHDID and higher.

In an embryofetal development study in pregnant rabbits, orally dosed during the period of organogenesis from gestation days 6 to 18, glycopyrrolate administration produced no structural

abnormalities or effects on fetal survival at the highest tested dose that was 50 times the MRHDID . Maternal toxicity was characterized by abortions at doses 18 times the MRHDID and higher.

### TRIMBOW

In an embryofetal development study in pregnant rats orally dosed during organogenesis from gestation days 6 to 17, TRIMBOW (BDP/FF/GB ratio 100/6/25 mg/kg/day) produced reduction in fetal weights and increased incidence of visceral variations at doses 83 and 0.8 times the MRHDID and higher for BDP (metabolite- B17MP) and FF, respectively.

In a pre- and post-natal development study, pregnant female rats received TRIMBOW (BDP/FF/GB ratio 100/6/25 mg/kg/day) from gestation day 6 through prenatal day 21. Maternal toxicity included mortalities in females during gestation. Increased post-implantation loss, reduced litter sizes and decreased pup survival were observed at doses 1.9, 3.7, and 7.7 times the MRHDID (based on mcg/m<sup>2</sup>) for beclomethasone, formoterol fumarate, and glycopyrrolate, respectively. F1 generation pups showed reduction in corpora lutea leading to increase in post-implantation loss and reduced mean litter size at 1.9, 3.7, and 7.7 times the MRHDID (based on mg/m<sup>2</sup>) for beclomethasone, formoterol fumarate, and glycopyrrolate, respectively.

## **8.2 Lactation**

### Risk Summary

There are no data available on the presence of beclomethasone dipropionate, formoterol fumarate or glycopyrrolate in human milk; the effects on the breastfed child; or the effects on milk production. Glucocorticoids are excreted in human milk. It is reasonable to assume that beclomethasone dipropionate and its metabolites are also excreted in human milk. Formoterol is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Anticholinergics like glycopyrrolate could suppress lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRIMBOW and any potential adverse effects on the breast-fed child from TRIMBOW or from the underlying maternal condition.

## **8.3 Females and Males of Reproductive Potential**

### Beclomethasone Dipropionate

Impairment of fertility was observed in rats and dogs at oral doses of beclomethasone dipropionate corresponding to 250 and 25 times the MRHDID for adults on a mg/m<sup>2</sup> basis, respectively [see *Nonclinical Toxicology (13.1)*].

### TRIMBOW

A reduction of conception rate, fertility index, slight increase in mean precoital time, significant reduction in corpora lutea, and increased pre-implantation loss were identified in female rats treated with TRIMBOW at an oral dose 187, 367, 767 times the MRHDID for BDP, FF, and G components, respectively, based on mg/m<sup>2</sup>. No effects on male fertility were noted [see *Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

The safety and effectiveness of TRIMBOW have not been established in pediatric patients.

## **8.5 Geriatric Use**

Of the total number of TRIMBOW-treated patients in clinical studies for asthma, 204 (18%) were 65 years of age and older [see *Clinical Studies (14)*]. No overall differences in safety or effectiveness

were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients.

## 8.6 Hepatic Impairment

Formal pharmacokinetic studies using TRIMBOW have not been conducted in patients with hepatic impairment. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, patients with severe hepatic disease should be closely monitored.

## 8.7 Renal Impairment

Glycopyrronium systemic exposure is increased in patients with severe renal impairment (eGFR <15 mL/min/1.73 m<sup>2</sup>) [see *Clinical Pharmacology* (12.3)]. In patients with severe renal impairment or end-stage renal disease (eGFR <15 mL/min/1.73 m<sup>2</sup>) requiring dialysis, TRIMBOW should only be used if the expected benefit outweighs the potential risk.

## 10 OVERDOSAGE

TRIMBOW contains beclomethasone dipropionate, formoterol fumarate, and glycopyrrolate; therefore, the risks associated with overdosage for the individual components described below apply to TRIMBOW. Treatment of overdosage consists of discontinuation of TRIMBOW together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

### Beclomethasone Dipropionate

If used at excessive doses for prolonged periods, systemic corticosteroid effects, such as hypercorticism may occur [see *Warnings and Precautions* (5.7)].

### Formoterol Fumarate

The signs and symptoms with overdosage of formoterol fumarate are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol fumarate.

### Glycopyrrolate

High doses of glycopyrrolate, a component of TRIMBOW, may lead to anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadedness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation, or difficulties in voiding.

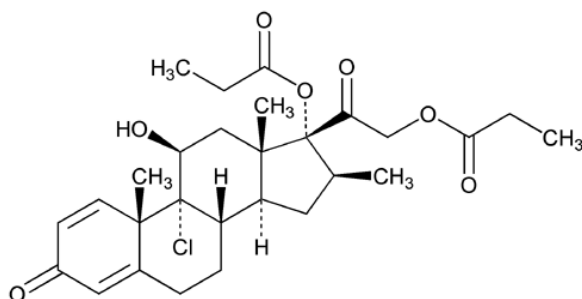
## 11 DESCRIPTION

TRIMBOW (beclomethasone dipropionate, formoterol fumarate and glycopyrrolate) Inhalation Aerosol is a pressurized metered-dose inhaler that delivers a combination of beclomethasone dipropionate [an inhaled corticosteroid (ICS)], formoterol fumarate [an inhaled long-acting beta<sub>2</sub>-adrenergic agonist (a LABA)] and glycopyrrolate (an anticholinergic) for oral inhalation.

Beclomethasone dipropionate, an inhaled corticosteroid [ICS], has the chemical name [2-[(8S,9R,10S,11S,13S,14S,16S,17R)-9-chloro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-propanoyloxy-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] propanoate. Beclomethasone dipropionate is a white to creamy white, odorless powder, insoluble in

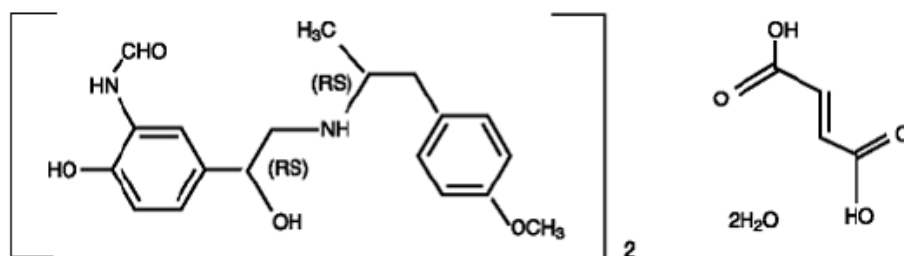
water, freely soluble in acetone, and sparingly soluble in alcohol, with a molecular weight of 521.04218 g/mol, and the molecular formula is  $C_{28}H_{37}ClO_7$ .

The structural formula is as follows:



Formoterol fumarate, a long-acting  $\beta_2$  agonist has the chemical name (E)-but-2-enedioic acid; N-[2-hydroxy-5-[(1*R*)-1-hydroxy-2-[(1*R*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. Formoterol fumarate has a molecular weight of 840.91 g/mol, and the molecular formula is  $C_{42}H_{52}N_4O_{12}$ .

The structural formula is as follows:

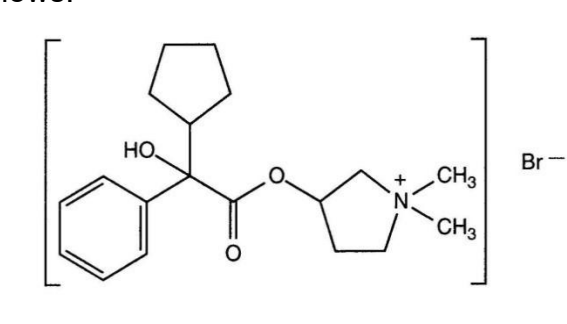


Formoterol fumarate contains two chiral centers and consists of a single enantiomeric pair (a racemate of *R,R* and *S,S*).

Glycopyrrolate is a quaternary ammonium bromide salt with the following chemical name: [*RS*]-3-[(*SR*)-(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-Pyrrolidinium bromide. Two asymmetric atoms of carbon are present in the molecule: Glycopyrrolate is represented by the (*R,S*)-(*S,R*) racemic pair of enantiomers, corresponding to the threo diastereoisomeric structure.

Glycopyrrolate is a powder that is freely soluble in water. Glycopyrrolate has a molecular weight of 398.33 g/mol, and the molecular formula is  $C_{19}H_{28}BrNO_3$ .

The structural formula is as follows:



Glycopyrrolate contains two chiral centers and is a racemate of a 1;1 mixture of the R,S and S,R diastereomers. The active moiety, glycopyrronium, is the positively charged ion of glycopyrrolate.

TRIMBOW 86 mcg/4.9 mcg/10.6 mcg and TRIMBOW 172 mcg/4.9 mcg/10.6 mcg are formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized, metered-dose inhalers, each containing 120 actuations. The canister is supplied with a grey plastic actuator with an integrated dose counter mechanism and mouthpiece, and a red cap (TRIMBOW 86 mcg/4.9 mcg/10.6 mcg) or a green cap (TRIMBOW 172 mcg/4.9 mcg/10.6 mcg). As a solution, TRIMBOW does not need to be shaken before use. TRIMBOW should be “primed” by actuating 2 times prior to using the first dose from a new canister. If the inhaler has not been used for 30 days or longer, re-prime the inhaler [see *How Supplied/Storage and Handling (16)*]. After priming, each actuation meters 100 or 200 mcg of beclomethasone dipropionate, 6.0 mcg of formoterol fumarate (equivalent to 5.7 mcg of formoterol fumarate anhydrous), and 12.5 mcg of glycopyrrolate (equivalent to 10 mcg of glycopyrronium) in 73.8 mg of solution from the valve and delivers 86 or 172 mcg of beclomethasone dipropionate, 4.9 mcg of formoterol fumarate (equivalent to 4.2 mcg of formoterol fumarate anhydrous), and 10.6 mcg of glycopyrrolate (equivalent to 8.5 mcg of glycopyrronium) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as coordination of the device (metered dose inhaler [MDI]) actuation with the inhalation maneuver, inspiratory flow and peak inspiratory flow through the delivery system, which may vary in patients with asthma and other pulmonary diseases and conditions. Avoid spraying in the eyes or face while using TRIMBOW.

TRIMBOW contains dehydrated alcohol (18% v/v), HFA 134a, and hydrochloric acid as excipients in the formulation.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

TRIMBOW contains beclomethasone dipropionate, formoterol fumarate and glycopyrrolate. The mechanism of action described below for the individual components applies to TRIMBOW. These drugs represent three different classes of medications (an inhaled corticosteroid, a long-acting beta<sub>2</sub>-adrenergic agonist and an anticholinergic) that have different effects on clinical physiology.

#### Beclomethasone Dipropionate

Beclomethasone dipropionate is a corticosteroid demonstrating potent anti-inflammatory activity. The precise mechanism through which beclomethasone dipropionate effects asthma symptoms is not known. Corticosteroids have been shown to have multiple anti-inflammatory effects, inhibiting both inflammatory cells (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and release of inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines). These anti-inflammatory actions of corticosteroids contribute to their efficacy in asthma.

Beclomethasone dipropionate is a prodrug that is rapidly activated by hydrolysis to the active monoester, 17-monopropionate (17-BMP). Beclomethasone 17-monopropionate has been shown *in vitro* to exhibit a binding affinity for the human glucocorticoid receptor, which is approximately 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, 1.5 times that of budesonide and 25 times that of beclomethasone dipropionate. The clinical relevance of these findings is unknown.

## Formoterol Fumarate

Formoterol fumarate is a long-acting selective beta<sub>2</sub>-adrenergic agonist (beta<sub>2</sub>-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol fumarate has more than 200-fold greater agonist activity at beta<sub>2</sub>-receptors than at beta<sub>1</sub>-receptors.

Although beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may have cardiac effects.

The pharmacologic effects of beta<sub>2</sub>-adrenoceptor agonist drugs, including formoterol fumarate, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

## Glycopyrrolate

Glycopyrrolate is a long-acting antimuscarinic agent which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. In preclinical *in vitro* as well as *in vivo* studies, prevention of acetylcholine, ovalbumin, acetaldehyde and histamine-induced bronchoconstrictive effects was dose-dependent. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

## **12.2 Pharmacodynamics**

### Cardiac Electrophysiology

A randomized, double-blind, placebo controlled, single dose study in 95 healthy volunteers assessed the effect of beclomethasone dipropionate, formoterol fumarate, and glycopyrrolate (BDP/FF/G) on the heart rate corrected QT interval based on the Fridericia's correction (QTcF) using electrocardiographic monitoring.

The maximum mean (90% two-sided upper confidence bound) difference in QTcF from placebo after baseline correction was 4.4 (5.9) milliseconds and 11.8 (13.4) milliseconds for BDP/FF/G with 172 mcg/9.8 mcg/21.2 mcg of BDP/FF/G and 4 times the dose of 172 mcg/9.8 mcg/ 21.2 mcg of BDP/FF/G, respectively.

A dose-dependent increase in heart rate was also observed. The maximum mean (90% two-sided CI) difference in heart rate between BDP/FF/G and placebo after baseline-correction was 3.8 (2.3; 5.4) beats/min observed 10 min post-dose at 172 mcg/9.8 mcg/21.2 mcg of BDP/FF/G and 10.3 (9.3; 11.3) beats/min observed 2 h post-dose at 4 times the dose of 172 mcg/9.8 mcg/ 21.2 mcg of BDP/FF/G.

### HPA Axis Effects

The potential systemic effects of TRIMBOW on the HPA axis have not been evaluated.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that the systemic exposure to BDP/17-BMP at a single BDP/FF/G dose of 344 mcg/9.8 mcg/21.2 mcg was lower compared with the highest dose of a BDP MDI product (640 mcg administered as a single dose). Therefore, the systemic effects on HPA-axis of

BDP/17-BMP delivered from TRIMBOW would be expected to be no greater than that of a BDP MDI product.

### **12.3 Pharmacokinetics**

The systemic exposure of beclomethasone dipropionate and 17-BMP approximately doubles following a single dose (4 inhalations) of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg compared to a single dose (4 inhalations) of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg in healthy subjects. Meanwhile, the systemic exposure of formoterol and glycopyrrolate was generally similar between TRIMBOW 172 mcg/4.9 mcg/10.6 mcg and TRIMBOW 86 mcg/4.9 mcg/10.6 mcg after inhalation.

#### Absorption

##### *Beclomethasone dipropionate*

Following inhaled administration of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg in healthy subjects the median time to reach  $C_{max}$  was 5 minutes for beclomethasone dipropionate and 30 minutes for 17-BMP.

##### *Formoterol fumarate*

Following inhaled administration of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg in healthy subjects the median time to reach  $C_{max}$  was 5 minutes. As with drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate is swallowed and then absorbed from the gastrointestinal tract.

##### *Glycopyrrolate*

Following inhaled administration of TRIMBOW 86/4.9 mcg/10.6 mcg in healthy subjects the median time to reach  $C_{max}$  was 5 minutes. Following glycopyrrolate inhalation, the absolute bioavailability was 9.6% and 11.9% with or without oral ingestion of charcoal block, respectively, when compared to intravenous infusion.

#### Distribution

##### *Beclomethasone dipropionate*

Apparent volume of distribution at steady state for 17-BMP in subjects with asthma following inhaled administration of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg was estimated to be approximately 135 L, via population PK analysis. The in vitro protein binding for 17-BMP was reported to be 94% to 96% over the concentration range of 1000 to 5000 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of beclomethasone dipropionate or its metabolites.

##### *Formoterol fumarate*

Apparent volume of distribution at steady state in subjects with asthma following inhaled administration of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg was estimated to be approximately 1560 L, via population PK analysis. Plasma protein binding of formoterol fumarate is 61-64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin in vitro was 31% to 38% over a range of 5 to 500 ng/mL.

##### *Glycopyrrolate*

Apparent volume of distribution at steady state in subjects with asthma following inhaled administration of TRIMBOW 86 mcg/4.9 mcg/10.6 mcg was estimated to be approximately 3895 L, via population PK analysis. Glycopyrronium binding to plasma proteins was  $71 \pm 4\%$  over the range of 50-250 pg/mL.

## Elimination

### *Beclomethasone dipropionate*

Beclomethasone dipropionate is excreted in feces in the form of metabolites. Only negligible amounts of unchanged beclomethasone dipropionate and its metabolites have been detected in urine. The mean elimination half-life of beclomethasone dipropionate and 17-BMP in subjects with asthma following inhaled administration of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg was 0.3 hours and 5 hours, respectively.

### *Formoterol fumarate*

The excretion of formoterol in urine was studied in seventeen healthy subjects, as part of the investigation of the effect of renal impairment on the pharmacokinetics of inhaled TRIMBOW. In that study, 4.7% of the administered formoterol dose was excreted in urine as unchanged formoterol. The mean elimination half-life of formoterol in subjects with asthma following inhaled administration of TRIMBOW 172 mcg/4.9 mcg/10.6 mcg was 6.7 hours.

### *Glycopyrrolate*

The excretion of glycopyrrolate in urine was studied in seventeen healthy subjects, as part of the investigation of the effect of renal impairment on the pharmacokinetics of inhaled TRIMBOW. In that study, 7% of the inhaled dose was excreted in urine as unchanged glycopyrronium.

## Metabolism

### *Beclomethasone dipropionate*

Beclomethasone dipropionate is cleared very rapidly from the systemic circulation by metabolism mediated via esterases found in most tissues, with limited involvement of CYP450 enzymes. The main product of metabolism of beclomethasone dipropionate is the active metabolite 17-BMP. Minor inactive metabolites, beclomethasone 21-monopropionate and beclomethasone, are also formed.

### *Formoterol fumarate*

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. The liver appears to be the primary site of metabolism.

### *Glycopyrrolate*

Metabolism plays a minor role in the overall elimination of glycopyrronium. The *in vitro* metabolic pattern of glycopyrrolate in human liver microsomes and hepatocytes demonstrates the main metabolic reaction was the hydroxylation on the phenyl or cyclopentyl rings. CYP2D6 was found to be the primary enzyme responsible for glycopyrrolate metabolism.

## Specific Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, sex, or body weight on the pharmacokinetics of beclomethasone 17-monopropionate, formoterol fumarate or glycopyrronium.

### *Patients with Hepatic Impairment*

Dedicated studies of TRIMBOW evaluating effect of hepatic impairment on the pharmacokinetics of beclomethasone dipropionate, formoterol fumarate and glycopyrrolate were not conducted.

As formoterol fumarate is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe hepatic impairment.

### *Patients with Renal Impairment*

The effect of renal impairment on the exposure to beclomethasone dipropionate, formoterol and glycopyrronium was evaluated after single administration of inhaled TRIMBOW in subjects with mild, moderate and severe renal impairment (9, 7 and 9 subjects, respectively) in comparison with demographically matching healthy volunteers. Renal impairment did not result in clinically significant increases in systemic exposure to beclomethasone dipropionate, 17-BMP, or formoterol fumarate. For glycopyrronium, there was no clinically significant increases in systemic exposure 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 < 30 mL/min/1.73 m<sup>2</sup>).

### Drug Interaction Studies

No pharmacokinetic interaction has been observed between beclomethasone dipropionate, formoterol fumarate and glycopyrrolate, when administered in combination by the inhaled route. Specific drug interaction studies of TRIMBOW with other co-administered drugs have not been performed.

*Cimetidine*: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes and an inhibitor of organic cation transport, had no clinically significant interactions with TRIMBOW.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No studies of carcinogenicity or mutagenicity were conducted with TRIMBOW; however, separate studies of beclomethasone dipropionate, formoterol fumarate and glycopyrrolate are described below.

#### *Beclomethasone dipropionate*

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment-related increases in the incidence of tumors in this study at the highest dose, which is approximately 30 times the MRHDID in adults on a mg/m<sup>2</sup> basis.

Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese hamster ovary (CHO) cells *in vitro*. No significant clastogenic effect was seen in cultured CHO cells *in vitro* or in the mouse micronucleus test *in vivo*.

#### *Formoterol fumarate*

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study, but not at dietary doses up to 5 mg/kg (AUC exposure approximately 450 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg and above (AUC exposure at the low dose of 0.5 mg/kg was approximately 45 times human exposure at the maximum recommended daily inhalation dose). This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg and above in the drinking water study, but not at doses up to 50 mg/kg (AUC

exposure approximately 590 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females and 50 mg/kg in males, but not at doses up to 5 mg/kg in either males or females (AUC exposure approximately 60 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg and above (AUC exposure at the low dose of 2 mg/kg was approximately 25 times human exposure at the maximum recommended daily inhalation dose). Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

### *Glycopyrrolate*

There was no evidence of treatment-related increases in the incidence of tumors in an oral 26-week carcinogenicity study in transgenic Tg-rasH2 mice and in a 2-year inhalation study in rats at up to 81 times the MRHDID in adults on a mg/m<sup>2</sup> basis.

Glycopyrrolate was not mutagenic or clastogenic in the following tests: Ames assay in bacterial and mammalian cells, chromosomal aberrations in mammalian cells, and micronucleus tests in mice and rats.

### Impairment of Fertility

#### *Beclomethasone Dipropionate*

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 250 times the MRHDID in adults on a mg/m<sup>2</sup> basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 25 times the MRHDID in adults on a mg/m<sup>2</sup> basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 17 times the MRHDID in adults on a mg/m<sup>2</sup> basis).

#### *TRIMBOW*

In a fertility and reproduction study, male rats were orally dosed for at least 6 weeks and females for 2 weeks prior to pairing, throughout the mating period, and up to gestation day 7. TRIMBOW (BDP/FF/GB ratio 100/6/25 mg/kg/day) caused reduction of conception rate and fertility index, a slight increase in mean precoital time, reduction in the number of corpora lutea, increased pre- and post-implantation loss, and reduction in the number of live embryos at doses 19, 37, and 77 times the MRHDID for BDP, FF, and G components, respectively (based on mg/m<sup>2</sup> at oral dose of 2,000 mcg/kg or higher). No effects on male fertility were noted.

## **14 CLINICAL STUDIES**

The efficacy of TRIMBOW was evaluated in two randomized, double-blind, parallel-group, active-controlled trials (TRIMARAN [NCT02676076] and TRIGGER [NCT02676089]) of 52 weeks duration in adult patients with asthma.

In TRIMARAN and TRIGGER, patients with an Asthma Control Questionnaire (ACQ-7) score  $\geq 1.5$  on their current asthma combination therapy of medium- or high-dose ICS plus a LABA entered a 2-week

run-in period of treatment with a dose of beclomethasone dipropionate/formoterol fumarate (BDP/FF) 172 mcg/9.8 mcg (TRIMARAN) or 344 mcg/9.8 mcg (TRIGGER) administered by oral inhalation twice daily. Only patients who remained inadequately controlled with an ACQ-7 score  $\geq 1.5$  after the run-in period were randomized.

In TRIMARAN, patients were randomized 1:1 to a dose of TRIMBOW 172 mcg/9.8 mcg/21.2 mcg or BDP/FF 172 mcg/9.8 mcg, both administered by oral inhalation twice daily. In TRIGGER, patients were randomized 1:1 to a dose of TRIMBOW 344 mcg/9.8 mcg/21.2 mcg or BDP/FF 344 mcg/9.8 mcg, both administered by oral inhalation twice daily. The efficacy population consisted of 2291 patients who received at least 1 dose of TRIMBOW or BDP/FF and had at least 1 post-baseline evaluation of efficacy in TRIMARAN (N = 1149) and TRIGGER (N = 1142).

Across the treatment groups in TRIMARAN and TRIGGER, most patients were female (61%), White (99.9%), and had never smoked (86%), with a mean age of 53 years (range: 18 to 75 years), a mean asthma duration of 25 years (range: 1 to 67 years), and past smokers (14%) having an average smoking history of 4.6 pack-years. The trials excluded patients who were current smokers. All patients had at least one documented asthma exacerbation (requiring treatment with systemic corticosteroids or an emergency department visit or in-patient hospitalization) in the 12 months prior to screening.

Across the treatment groups in TRIMARAN and TRIGGER, the mean pre-bronchodilator percent predicted FEV<sub>1</sub> was 53.6% (SD: 12.9%), the mean percent reversibility was 32.6% (SD: 21.9%), the mean absolute reversibility was 496 mL (SD: 283 mL), and the mean ACQ-7 score was 2.69 (SD: 0.61) at screening; at randomization, the mean ACQ-7 score was 2.36 (SD: 0.54) and the mean trough percent predicted FEV<sub>1</sub> was 58.5% (SD: 12.5%).

### Lung Function

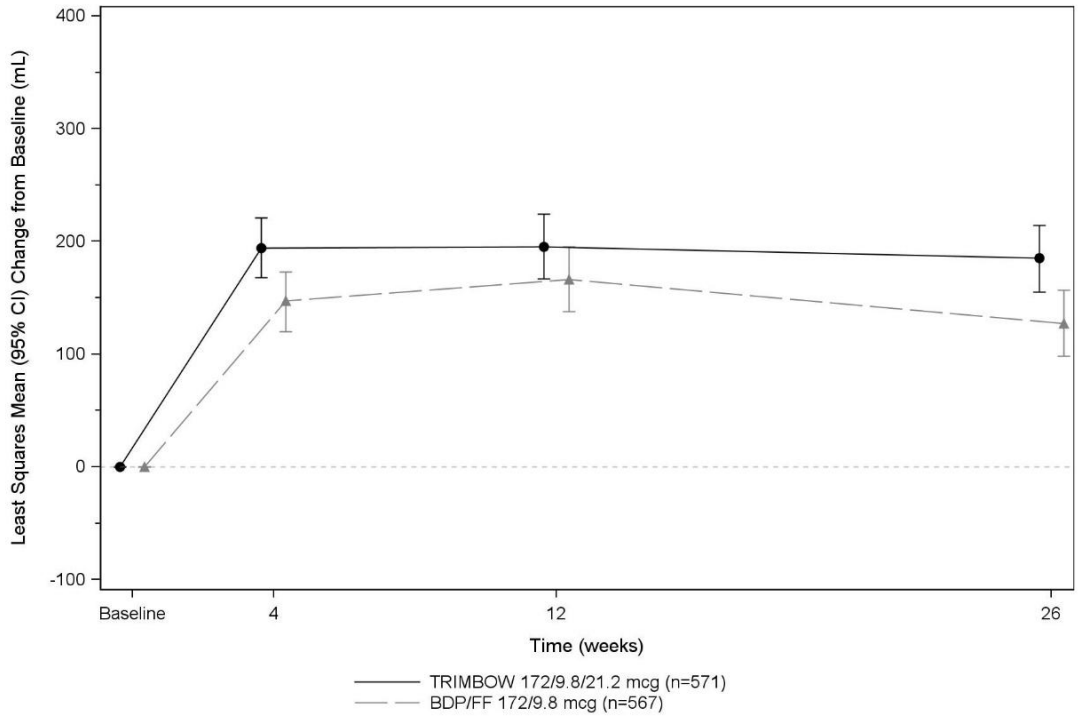
In TRIMARAN and TRIGGER, the efficacy of TRIMBOW was measured by the mean change from baseline in trough FEV<sub>1</sub> at Week 26. Patients treated with TRIMBOW at doses of 172 mcg/9.8 mcg/21.2 mcg and 344 mcg/9.8 mcg/21.2 mcg by oral inhalation twice daily showed improvements in the mean change from baseline in trough FEV<sub>1</sub> at Week 26 compared with BDP/FF at doses of 172 mcg/9.8 mcg and 344 mcg/9.8 mcg by oral inhalation twice daily, respectively (Table 3, Figures 1 and 2).

**Table 3. Least Squares Mean Change from Baseline in Trough FEV<sub>1</sub> (mL) at Week 26**

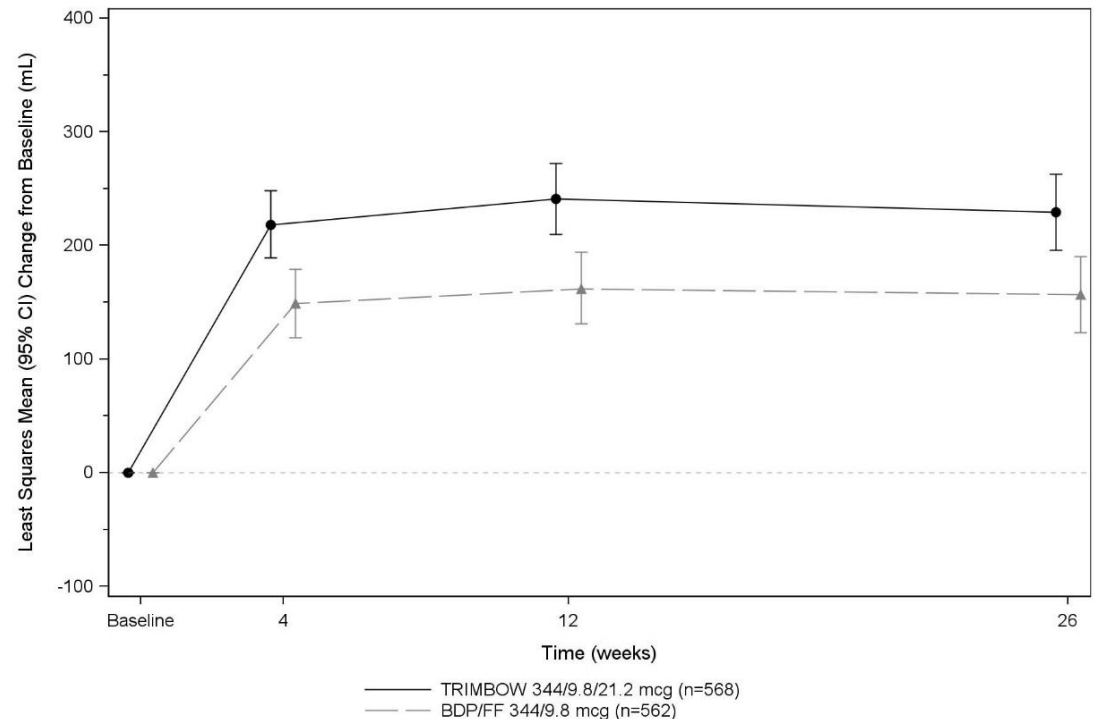
	TRIMARAN		TRIGGER	
	TRIMBOW 172/9.8/21.2 mcg twice daily (N=575)	BDP/FF 172/9.8 mcg twice daily (N=574)	TRIMBOW 344/9.8/21.2 mcg twice daily (N=571)	BDP/FF 344/9.8 mcg twice daily (N=571)
n (%)	571 (99)	567 (99)	568 (99)	562 (98)
LS mean change (95% CI)	185 (155, 214)	127 (98, 157)	229 (196, 263)	157 (123, 190)
TRIMBOW vs. BDP/FF Difference in LS means (95% CI)	57 (15, 99)		73 (26, 120)	

BDP/FF = beclomethasone dipropionate/formoterol fumarate, CI = confidence interval, FEV<sub>1</sub> = forced expiratory volume in 1 second, LS = least squares, mcg = micrograms, N = number of patients in the intent-to-treat population; n = number of patients included in the analysis

**Figure 1. Least Squares Mean Change from Baseline in Trough FEV<sub>1</sub> (mL) with TRIMBOW 172 mcg/9.8 mcg/21.2 mcg Twice Daily over 26 Weeks (TRIMARAN)**



**Figure 2. Least Squares Mean Change from Baseline in Trough FEV<sub>1</sub> (mL) with TRIMBOW 344 mcg/9.8 mcg/21.2 mcg Twice Daily over 26 Weeks (TRIGGER)**



The difference in the mean change from baseline in trough FEV<sub>1</sub> at Week 26 for TRIMBOW at doses of 172 mcg/9.8 mcg/21.2 mcg and 344 mcg/9.8 mcg/21.2 mcg by oral inhalation twice daily compared with BDP/FF at doses of 172 mcg/9.8 mcg and 344 mcg/9.8 mcg by oral inhalation twice daily was 57 mL (95% CI: 15, 99) and 73 mL (95% CI: 26, 120), respectively.

### Health-Related Quality of Life

At Week 52, the ACQ-7 responder rate (defined as a decrease in score of  $\geq 0.5$  from baseline) for TRIMBOW at doses of 172 mcg/9.8 mcg/21.2 mcg and 344 mcg/9.8 mcg/21.2 mcg by oral inhalation twice daily was 61% and 62%, respectively, compared with 59% and 58% for BDP/FF at doses of 172 mcg/9.8 mcg and 344 mcg/9.8 mcg by oral inhalation twice daily, resulting in odds ratios of 1.07 (95% CI: 0.84, 1.36) for TRIMBOW 172 mcg/9.8 mcg/21.2 mcg compared with BDP/FF 172 mcg/9.8 mcg and 1.12 (95% CI: 0.94, 1.32) for TRIMBOW 344 mcg/9.8 mcg/21.2 mcg compared with BDP/FF 344 mcg/9.8 mcg.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

TRIMBOW (beclomethasone dipropionate/formoterol fumarate/glycopyrrolate) Inhalation Aerosol:

- TRIMBOW 86 mcg/4.9 mcg/10.6 mcg: is supplied as a pressurized aluminum container, a grey plastic actuator with the dose counter on the back, a grey mouthpiece and a red cap.
- TRIMBOW 172 mcg/4.9 mcg/10.6 mcg: is supplied as a pressurized aluminum container, a grey plastic actuator with the dose counter on the back, a grey mouthpiece and a green cap.

Each pressurized container of TRIMBOW is packaged in a carton containing one canister, one actuator, a Patient Information leaflet, and the Instructions for Use.

TRIMBOW is available as presented in Table 4.

**Table 4 Package Information for TRIMBOW**

<b>Strength (beclomethasone dipropionate/formoterol fumarate/glycopyrrolate)</b>	<b>Number of Actuations per Canister</b>	<b>Net Fill Weight</b>	<b>NDC</b>
86 mcg/4.9 mcg/10.6 mcg	120	11.8 grams	NDC 10122-120-02
172 mcg/4.9 mcg/10.6 mcg	120	11.8 grams	NDC 10122-121-02

The TRIMBOW container should only be used with the TRIMBOW actuator, and the TRIMBOW actuator should not be used with any other inhalation drug product.

Prime the inhaler according to [Instructions for Use](#). If the inhaler has not been used for 30 days or longer, re-prime the inhaler by releasing 2 actuations (puffs) into the air, away from the face and eyes, before use.

### Dose Counter

TRIMBOW has a dose counter attached to the canister. The counter starts at 122 and counts down each time a spray is released. The correct amount of medication in each actuation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. The inhaler should be discarded when the counter reads 000 or if 2 months have passed since first use date, whichever comes first.

### Contents under Pressure

Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 122°F may cause bursting. Never throw container into fire or incinerator.

Keep out of reach of children. Do not spray into eyes.

Storage:

Prior to first use: Store refrigerated at 36°F to 46°F (2°C to 8°C).

After first use: Store the inhaler below 77°F (25°C) for a maximum of two months.

Do not freeze. Do not expose to temperatures higher than 122°F (50°C) as this may cause bursting.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

### Serious Asthma-Related Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used together, such as with TRIMBOW, there is not a significant increase in the risk of these events [See *Warnings and Precautions (5.1)*].

### Not for Acute Symptoms

Inform patients that TRIMBOW is not meant to relieve acute symptoms of asthma and extra doses should not be used for that purpose [see *Warnings and Precautions (5.2)*]. Advise patients to treat acute symptoms with an inhaled, short-acting beta<sub>2</sub>-agonist/corticosteroid or short-acting beta<sub>2</sub>-agonist. Provide patients with such medication and instruct them how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonist/corticosteroid combination, or inhaled, short-acting beta<sub>2</sub>-agonists
- Need for more inhalations than usual of inhaled, short acting beta<sub>2</sub>-agonists/corticosteroid combination, or inhaled short acting beta<sub>2</sub>-agonists
- Significant decrease in lung function as outlined by the healthcare provider

Tell the patient they should not stop therapy with TRIMBOW without physician/provider guidance since symptoms may recur after discontinuation [See *Warnings and Precautions (5.2)*].

### Avoid Use of Additional Long-acting Beta<sub>2</sub>-agonists

Instruct patients not to use other LABA drugs for asthma [See *Warnings and Precautions (5.3)*].

### Oropharyngeal Candidiasis

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx (i.e., thrush) in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with TRIMBOW, but at times therapy with TRIMBOW may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush [See *Warnings and Precautions (5.4)*].

### Immunosuppression and Risk of Infections

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex [See *Warnings and Precautions (5.5)*].

### Hypercorticism and Adrenal Suppression

Advise patients that TRIMBOW may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to TRIMBOW [See *Warnings and Precautions* (5.7)].

### Paradoxical Bronchospasm

As with other inhaled medicines, TRIMBOW can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue TRIMBOW and contact their healthcare provider right away [See *Warnings and Precautions* (5.8)].

### Hypersensitivity Reactions, including Anaphylaxis

Advise patients that hypersensitivity reactions have been reported after administration. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips and face), urticaria or skin rash, instruct patients to discontinue TRIMBOW immediately [See *Warnings and Precautions* (5.9)].

### Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk [See *Warnings and Precautions* (5.11)].

### Ocular Effects such as Cataracts or Glaucoma

Inform patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations. Instruct patients to 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 physician immediately if any of these signs or symptoms develop [See *Warnings and Precautions* (5.12)].

### Worsening of Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately if any of these signs or symptoms develop [See *Warnings and Precautions* (5.13)].

### Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a health care practitioner immediately should any of these signs and symptoms develop [See *Warnings and Precautions* (5.10)].

Manufactured for:  
Chiesi USA, Inc.  
Cary, NC 27518  
USA



Manufactured by:  
Chiesi Farmaceutici, S.p.A.  
43122 Parma, Italy

TRIMBOW is a trademark of CHIESI FARMACEUTICI S.P.A..  
CTT-001-0226-00-W

**PATIENT INFORMATION**  
**TRIMBOW® (trim-bow)**  
**(beclomethasone dipropionate, formoterol fumarate and glycopyrrolate)**  
**inhalation aerosol, for oral inhalation use**

**What is TRIMBOW?**

- TRIMBOW combines 3 medicines in 1 inhaler, an inhaled corticosteroid (ICS) medicine (beclomethasone dipropionate), a long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicine (formoterol fumarate) and an anticholinergic medicine (glycopyrrolate).
- ICS medicines like beclomethasone dipropionate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
- LABA medicines such as formoterol fumarate and anticholinergic medicines such as glycopyrrolate help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- TRIMBOW is a prescription medicine used long term (chronic) to prevent and control symptoms of asthma for better breathing and prevent symptoms such as wheezing.
- **TRIMBOW is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- TRIMBOW contains formoterol fumarate. LABA medicines such as formoterol fumarate when used alone increase the risk of hospitalizations and death from asthma problems. TRIMBOW contains an ICS, a LABA and an anticholinergic. When an ICS and LABA are used together, there is **not** a significant increased risk in hospitalizations and death from asthma problems.

**TRIMBOW should not be used in children.**

It is not known if TRIMBOW is safe and effective in children.

**Do not use TRIMBOW:**

- to treat sudden, severe symptoms of asthma.
- if you are allergic to beclomethasone dipropionate, formoterol fumarate, glycopyrrolate or any of the ingredients in TRIMBOW. See the end of this Patient Information for a [complete list of ingredients in TRIMBOW](#).

**Before using TRIMBOW, tell your healthcare provider about all of your medical conditions, including if you:**

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have kidney problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma, increased pressure in your eye, cataracts, blurred vision, or other changes in vision. TRIMBOW may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. TRIMBOW may make these problems worse.
- have any type of viral, bacterial, parasitic, or fungal infection.
- are exposed to chickenpox or measles.
- are pregnant or plan to become pregnant. It is not known if TRIMBOW may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicines in TRIMBOW pass into your breast milk and if they can harm your baby.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TRIMBOW and certain other medicines may affect each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- anticholinergics (including tiotropium, ipratropium, aclidinium)
- atropine
- other LABA (including salmeterol, formoterol fumarate, arformoterol, vilanterol, olodaterol, and indacaterol)
- antifungal or anti-HIV medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### How should I use TRIMBOW?

Read the step-by-step instructions for using TRIMBOW at the end of this Patient Information.

- **Do not** use TRIMBOW unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- TRIMBOW comes in 2 different strengths. Your healthcare provider prescribed the strength that is best for you.
- If you have been using a different inhaler containing beclomethasone dipropionate previously, ask your healthcare provider for advice, as the effective dose of beclomethasone dipropionate in TRIMBOW for the treatment of your asthma may be lower than that of some other inhalers.
- Use TRIMBOW exactly as your healthcare provider tells you to use it. Do not use TRIMBOW more often than prescribed.
- Use 2 inhalations of TRIMBOW, 2 times each day (2 puffs in the morning and 2 puffs in the evening).
- If you miss a dose of TRIMBOW, take it as soon as you remember. Take your next dose at your usual time. Do not take more than 4 inhalations per day.
- If you take too much TRIMBOW, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA or an anticholinergic for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA or anticholinergic medicines.
- **Do not** stop using TRIMBOW unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **TRIMBOW does not relieve sudden symptoms of asthma and you should not take extra doses of TRIMBOW to relieve these sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.

### What are the possible side effects of TRIMBOW?

TRIMBOW can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using TRIMBOW to help reduce your chance of getting thrush.
- **weakened immune system and increased chance of getting infections (immunosuppression).**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an ICS (such as TRIMBOW). During this transition period, when your body is under stress from fever, trauma (such as a car accident), infection, surgery, or worse asthma symptoms, adrenal insufficiency can get worse and may cause death. Symptoms of adrenal insufficiency include:
  - feeling tired
  - lack of energy
  - weakness
  - nausea and vomiting
  - low blood pressure (hypotension)
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop using TRIMBOW and call your healthcare provider right away.
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth and tongue
  - breathing problems
- **effects on heart.**
  - increased blood pressure
  - a fast or irregular heartbeat, awareness of heartbeat
  - chest pain
- **effects on nervous system.**
  - tremor
  - nervousness
- **bone thinning or weakness (osteoporosis).**

- **eye problems** including glaucoma, increased pressure in your eye, cataracts, blurred vision, worsening of narrow-angle glaucoma, or other changes in vision. You should have regular eye exams while using TRIMBOW.

Acute narrow-angle glaucoma can cause permanent loss of vision if not treated. Symptoms of acute narrow-angle glaucoma may include:

- eye pain or discomfort
- nausea or vomiting
- blurred vision
- seeing halos or bright colors around lights
- red eyes

If you have these symptoms, call your healthcare provider right away before taking another dose.

- **urinary retention.** People who take TRIMBOW may develop new or worse urinary retention. Symptoms of urinary retention may include:

- difficulty urinating
- painful urination
- urinating frequently
- urination in a weak stream or drips

If you have these symptoms of urinary retention, stop taking TRIMBOW, and call your healthcare provider right away before taking another dose.

- **changes in laboratory blood values**, including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia).
- **slowed growth in children.**

#### The most common side effects of TRIMBOW include:

- bronchitis
- high blood pressure
- back pain
- hoarseness or laryngitis
- upper respiratory tract infection (such as itchy, runny or blocked nose, inflammation of the nasal lining, sore throat)
- flu
- low red blood cells (anemia)
- muscle spasms
- mouth and throat pain
- inflammation of the sinuses

These are not all the possible side effects of TRIMBOW.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Chiesi USA, Inc. at 1-888-661-9260.

#### How should I store TRIMBOW?

- Before first use: Store TRIMBOW in a refrigerator between 36°F to 46°F (2°C to 8°C).
- After first use: Store TRIMBOW below 77°F (25°C) for a maximum of 2 months.
- Throw away TRIMBOW 2 months after you remove it from the refrigerator, or when the dose counter reaches zero "0", whichever comes first.
- **Do not** put a hole in the TRIMBOW canister.
- **Do not** throw the canister into a fire or incinerator.
- **Do not** use or store it near heat or open flame. Temperatures higher than 122°F (50°C) may cause bursting.
- **Do not** freeze TRIMBOW.

**Keep TRIMBOW and all medicines out of the reach of children.**

#### General information about the safe and effective use of TRIMBOW.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TRIMBOW for a condition for which it was not prescribed. Do not give TRIMBOW to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about TRIMBOW that is written for health professionals.

#### What are the ingredients in TRIMBOW?

**Active ingredients:** beclomethasone dipropionate, formoterol fumarate and glycopyrrolate

**Inactive ingredients:** dehydrated alcohol, hydrochloric acid, and hydrofluoroalkane (HFA 134a)

Manufactured by:  
Chiesi Farmaceutici S.p.A.  
43122 Parma, Italy

Manufactured for:  
Chiesi USA, Inc.  
Cary, NC 27518  
USA  
1-888-661-9260

All trademarks referenced herein are the property of their prospective owners.  
CTT-002-0226-00-W

For more information about TRIMBOW, call 1-888-661-9260.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Approved: 05/2026

# INSTRUCTIONS FOR USE

## TRIMBOW® (trim-bow)

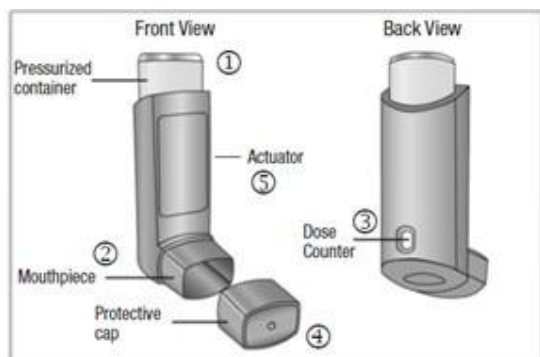
(beclomethasone dipropionate, formoterol fumarate and glycopyrrolate)  
inhalation aerosol, for oral inhalation use

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

**TRIMBOW** is available in one size providing 120 puffs.

### Parts of your inhaler (See Figure A)

- The pressurized container (1) fits into an actuator (5) and holds the medicine.
- The mouthpiece (2) delivers the medicine from the pressurized container (1).
- The dose counter (3) shows how many doses are left. Each time you press the pressurized container (1), a puff of medicine is released, and the dose counter will count down by 1.
- The protective cap (4) covers the mouthpiece when the inhaler is not in use.



**Figure A**

### Important information you need to know before using TRIMBOW

#### For oral inhalation use only

- Take 2 inhalations of medicine in the morning and 2 inhalations of medicine in the evening.
- Use the pressurized container only with the actuator supplied with TRIMBOW.
- Do not use parts of the TRIMBOW inhaler with parts from any other inhalation medicine.

#### Do not remove the pressurized container from the actuator because:

- You may not receive the correct amount of medicine.
- The dose counter may not function.
- Reinsertion may cause the dose counter to count down by 1 and may discharge a puff.

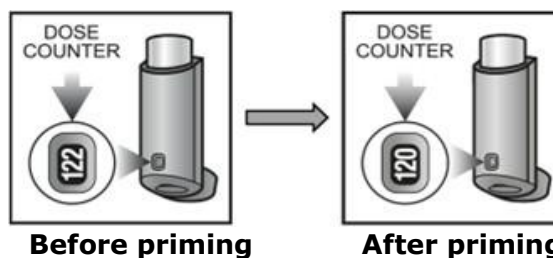
Never try to change the numbers on the dose counter or remove the dose counter from the actuator.

### Preparing to use TRIMBOW

Write the date you first use TRIMBOW on the carton box. Check 2 months have not passed since the first use date. If more than 2 months have passed, throw away your inhaler.

**Before using the inhaler for the first time, you must prime it 2 times** to make sure that it is working properly.

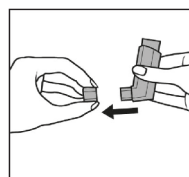
1. Check that the dose counter displays 122 doses (**See Figure B**).
2. Remove the protective cap from the mouthpiece.
3. Hold your inhaler in the upright position with the mouthpiece at the bottom.
4. Point the mouthpiece away from your face and firmly press the pressurized container 2 times to release 2 puffs.
5. Check the dose counter. After priming, the dose counter should display 120 remaining doses (**See Figure B**).



**Before priming**  
**Figure B**

**After priming**

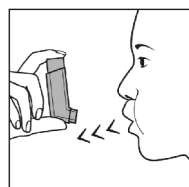
### How to use your inhaler



**Figure C**

#### Step 1.

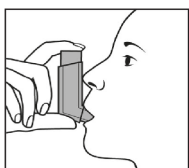
Remove the protective cap from the mouthpiece and check that the mouthpiece is clean and does not have any foreign objects (**See Figure C**).



**Figure D**

#### Step 2.

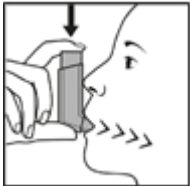
Breathe out as slowly and fully as you comfortably can through your mouth to empty your lungs (**See Figure D**). Do not breathe into the inhaler.



**Figure E**

#### Step 3.

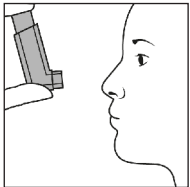
Hold the inhaler upright with the mouthpiece at the bottom and place the mouthpiece into mouth and close lips around the mouthpiece (**See Figure E**). Avoid spraying the inhaler towards the eyes. If spray enters eyes, rinse with water and get medical advice if irritation continues.



**Figure F**

**Step 4.**

Breathe in slowly and deeply through your mouth to fill your lungs with air and at the same time, press down firmly and fully on the top of the pressurized container until it stops moving in the actuator (See Figure F). Take your finger off the pressurized container.



**Figure G**

**Step 5.**

When you have finished breathing in, hold your breath as long as you can, up to 10 seconds. Then, remove the inhaler from your mouth and breathe out slowly through your nose, while keeping your lips closed (See Figure G). Do not breathe out through your inhaler.

**Step 6.**

Check the dose counter displays the number of puffs left in your inhaler.

**Step 7.**

Wait at least 30 seconds to take your second inhalation. Keep the inhaler in the upright position and repeat Step 2 to Step 6.

**After using your inhaler**

**Step 8.**

After use, replace the protective cap (See Figure H).

**Step 9.**

Rinse your mouth with water without swallowing it.

**When to get a new inhaler**

It is important that you pay attention to the number of puffs left in your inhaler by checking the dose counter.

You should get a refill when the dose counter shows the number 20. Stop using the inhaler when the dose counter reaches 0, as any medicine left in the inhaler may not be enough to give you a full dose.

**Cleaning your TRIMBOW inhaler**

The mouthpiece should be cleaned after every 7 days of use. It is very important to keep your inhaler clean so that medicine will not build up.

**Routine cleaning instructions**

- Do not remove the pressurized container from the actuator.
- Remove the protective cap from the mouthpiece.
- Wipe the inside and outside surfaces of the mouthpiece with a clean, dry, lint-free cloth or tissue.
- Do not use water or other liquids to clean your inhaler.
- Replace the protective cap on the mouthpiece after cleaning.

**Storing TRIMBOW**

**Before first use:**

Store TRIMBOW in a refrigerator between 36°F to 46°F (2°C to 8°C).

**After first use:**

Store TRIMBOW below 77°F (25°C) for a maximum of 2 months.

- Keep TRIMBOW and all medicines out of the reach of children.
- The inhaler can be stored in any position.
- Do not put a hole in or throw the container into a fire or incinerator. Do not use or store it near heat or open flame. Exposure to temperatures above 122°F (50°C) may cause bursting.
- If the inhaler has not been used for 30 days or longer, re-prime the inhaler by releasing 2 puffs into the air, away from the face and eyes, before use.
- Do not use this medicine after the expiration date which is stated on the label and carton after EXP. The expiration date means the last day of that month.
- Do not use this medicine more than 2 months after the first use date.

**Throwing away (Disposing of) TRIMBOW**

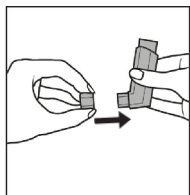
Throw the empty inhaler away in your household trash out of reach of children and pets.

Manufactured by:  
Chiesi Farmaceutici S.p.A.  
43122 Parma, Italy

Manufactured for:  
Chiesi USA, Inc.  
Cary, NC 27518 USA  
1-888-661-9260

TRIMBOW is registered in the US Patent and Trademark Office. All trademarks referenced herein are the property of their prospective owners. For more information about TRIMBOW, call 1-888-661-9260.

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Approved: 05/2026  
CTT-003-0226-00-W



**Figure H**