HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEVESPI AEROSPHERE safely and effectively. See full prescribing information for BEVESPI AEROSPHERE.

BEVESPI AEROSPHERE™ (glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use
Initial U.S. Approval: 2016

Boxed Warning, removed (1)

Indications and Usage (1)
Contraindications (4)
Warnings and Precautions (5.1)

DOSAGE AND ADMINISTRATION
- For oral inhalation only.
- Maintenance treatment of COPD: 2 inhalations of BEVESPI AEROSPHERE twice daily. (2)

Dosage Forms and Strengths
- Inhalation aerosol: Pressurized metered dose inhaler containing a combination of glycopyrrolate (9 mcg) and formoterol fumarate (4.8 mcg) as an inhalation aerosol.
- Two inhalations equal one dose. (3)

Contraindications
- Use of a LABA, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, without an inhaled corticosteroid is contraindicated in patients with asthma. (4)
- Hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of this product. (4, 5.5)

Warnings and Precautions
- LABA as monotherapy (without an inhaled corticosteroid) for asthma increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose. (5.3, 7.1)
- If paradoxical bronchospasm occurs, discontinue BEVESPI AEROSPHERE and institute alternative therapy. (5.4)
- Use with caution in patients with cardiovascular disorders. (5.6)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.7)
- Be alert to hypokalemia and hyperglycemia. (5.8)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur. (5.9)
- Worsening urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur. (5.10)

Most common adverse reactions (incidence ≥2% and more common than with placebo) include: urinary tract infection and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Other adrenergic drugs may potentiate effect: Use with caution (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium sparing diuretics may worsen with concomitant beta-agonists. (7.3)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of formoterol fumarate on cardiovascular system. (7.4)
- Beta-blockers: Use with caution and only when medically necessary. (7.5)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administrations of BEVESPI AEROSPHERE with other anticholinergic-containing drugs. (7.6)

USE IN SPECIFIC POPULATIONS
- Use in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk. (8.7)

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

Revised: 5/2019

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1. INDICATIONS AND USAGE

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitation of Use: BEVESPI AEROSPHERE is not indicated for the relief of acute bronchospasm or for the treatment of asthma [see Warnings and Precautions (5.1, 5.2)].

2. DOSAGE AND ADMINISTRATION

BEVESPI AEROSPHERE (glycopyrrolate/formoterol fumarate 9 mcg/4.8 mcg) should be administered as two inhalations taken twice daily in the morning and in the evening by the orally inhaled route. Two inhalations should take more than two inhalations twice daily.

BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator, which indicates how many inhalations remain. The dose indicator display will move after every tenth actuation. When nearing the end of the usable inhalations, the color behind the number in the dose indicator display window changes to red. BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows zero.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air from the face, shaking well before each spray. BEVESPI AEROSPHERE must be re-primed when the inhaler has not been used for more than 7 days. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air from the face, shaking well before each spray.

3. DOSAGE FORMS AND STRENGTHS

Inhalation Aerosol: BEVESPI AEROSPHERE is a pressurized metered dose inhaler that delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate per inhalation. Two inhalations equal one dose. BEVESPI AEROSPHERE contains 28 or 120 inhalations per canister. The canister has an attached dose indicator and is supplied with a white plastic actuator with an orange dust cap.

4. CONTRAINDICATIONS

Use of a long-acting beta-adrenergic agonist (LABA), including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, with an inhaled corticosteroid is contraindicated in patients with asthma [see Warnings and Precautions (5.1)]. BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

BEVESPI AEROSPHERE is contraindicated in patients with hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of the product [see Warnings and Precautions (5.5)].

5. WARNINGS AND PRECAUTIONS

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

- The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. BEVESPI AEROSPHERE is not indicated for the treatment of asthma [see Contraindications (4)].

- Use of LABA as monotherapy [without inhaled corticosteroids (ICS)] for asthma is associated with an increased risk of asthma-related death. Available data from community clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

- A 28-week, placebo-controlled US trial comparing the safety of another LABA (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. 3/13,176 in subjects treated with placebo; RR 4.37, 95% CI: 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of LABAs, including formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE.

- No trial adequate to determine whether the rate of asthma-related deaths is increased in patients treated with BEVESPI AEROSPHERE has been conducted.

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

5.2 Deterioration of Disease and Acute Episodes

BEVESPI AEROSPHERE should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. BEVESPI AEROSPHERE has not been studied in patients with acutely deteriorating COPD. The use of BEVESPI AEROSPHERE in this setting is inappropriate.

BEVESPI AEROSPHERE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BEVESPI AEROSPHERE 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-agonist.

When beginning BEVESPI AEROSPHERE, patients who have been taking inhaled, short-acting beta,-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these medicines and use them only for symptomatic relief of acute respiratory symptoms. When prescribing BEVESPI AEROSPHERE, the healthcare provider should make an evaluation of the patient’s history of inhaled, short-acting beta-agonist and instruct the patient on how it should be used. Increasing inhaled beta-agonist use is a signal of deterioration of disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BEVESPI AEROSPHERE no longer controls the symptoms of bronchospasm or dyspnea, or in the patient’s history, short-acting beta-agonist less effective, or the patient needs more inhalations of short-acting beta-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of BEVESPI AEROSPHERE beyond the recommended dose is not appropriate in this situation.

5.3 Excessive Use of BEVESPI and Use with Other Long-Acting Beta,-Agonists

As with other inhaled medicines containing beta,-agonists, BEVESPI AEROSPHERE should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABAs, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in connection with the excessive use of beta-agonist sympathomimetic medicines. Patients using BEVESPI AEROSPHERE should not use another medicine containing a LABA for any reason [see Drug Interactions (7.1)].

5.4 Paradoxical Bronchospasm

As with other inhaled medicines, BEVESPI AEROSPHERE can produce paradoxical bronchospasm which may be life-threatening. If paradoxical bronchospasm occurs, BEVESPI AEROSPHERE should be discontinued immediately, and alternative therapy should be instituted.

5.5 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions have been reported after administration of glycopyrrolate or formoterol fumarate, the components of BEVESPI AEROSPHERE. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips, and face), urticaria, or skin rash, BEVESPI AEROSPHERE should be stopped at once and alternative treatment should be considered.

5.6 Cardiovascular Effects

Formoterol fumarate, like other beta,-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms [see Clinical Pharmacology (12.2)]. If such effects occur, BEVESPI AEROSPHERE should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.7 Coexisting Conditions

BEVESPI AEROSPHERE, like all medications containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta,-agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoadiposis.

5.8 Hypokalemia and Hypermagnesemia

Beta,-agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see Clinical Pharmacology (12.2)]. The decrease in serum potassium is usually transient, not requiring supplementation. Beta,-agonist medicines may produce transient hypermagnesemia in some patients. In two clinical trials of 24-weeks and a 28-week safety extension study evaluating BEVESPI AEROSPHERE in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

5.9 Worsening of Narrow-Angle Glaucoma

BEVESPI AEROSPHERE should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should 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 should any of these signs or symptoms develop.

5.10 Worsening of Urinary Retention

BEVESPI AEROSPHERE 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 physician immediately should any of these signs or symptoms develop.

6. ADVERSE REACTIONS

LABAs, such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, as monotherapy (without an inhaled corticosteroid) for asthma increase the risk of asthma-related events. BEVESPI AEROSPHERE is not indicated for the treatment of asthma [see Warnings and Precautions (5.1)].

The following adverse reactions are described in greater detail elsewhere in the labeling:

- A 24-week, placebo-controlled bronchospasm trial (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV1) was 51% (range: 19% to 82%) and mean percent reversibility was 2% (range: 50% to 12%).

- A 24-week, placebo-controlled bronchospasm trial (Trials 1 and 2; n=2,100 and n=1,610, respectively). Of the 3,710 subjects, 56% were male and 91% were Caucasian. They had a mean age of 63 years and an average smoking history of 51 pack-years, with 54% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV1) was 51% (range: 19% to 82%) and mean percent reversibility was 2% (range: 50% to 12%).
Subjects received one of the following treatments: BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control.

Table 1 – Adverse Reactions with BEVESPI AEROSPHERE: 2% Incidence and More Common than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BEVESPI AEROSPHERE (n=1036)</th>
<th>Glycopyrrolate 18 mcg BID (n=890)</th>
<th>Formoterol Fumarate 9.6 mcg BID (n=890)</th>
<th>Placebo (n=443)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2.6</td>
<td>1.8</td>
<td>1.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Infections and infestation</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.0</td>
<td>3.0</td>
<td>2.7</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, pharyngitis, pain, vomiting, tinnitus, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

Long-Term Safety Extension Trial

In a 28-week long-term safety extension trial, 893 subjects who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks for a total treatment period of approximately 52 weeks with BEVESPI AEROSPHERE, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily or active control. Because the subjects continued from Trial 1 or Trial 2 into the safety extension trial, the demographic and baseline characteristics of the long-term safety extension trial were similar to those of the placebo-controlled efficacy trials described above. The adverse reactions reported in the long-term safety extension trial were consistent with those observed in the two long-term placebo-controlled trials. Additional Adverse Reactions: Other adverse reactions that have been associated with the component formoterol fumarate include: hypersensitivity reactions, hyperglycemia, sleep disturbance, agitation, restlessness, tremor, nausea, tachycardia, palpitations, cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia, and extrasystoles).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of BEVESPI AEROSPHERE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In postmarketing experience with BEVESPI AEROSPHERE, hypersensitivity and urinary retention have been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with BEVESPI AEROSPHERE.

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathomimetic effects of formoterol, a component of BEVESPI AEROSPHERE, 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 any hypokalemic effect of beta, adrenergic agonists such as formoterol, a component of BEVESPI AEROSPHERE.

7.3 Non-Potassium-Sparing Diuretics

The ECG 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. Approximately 17% of subjects were taking non-potassium-sparing diuretics during the two 24-week placebo-controlled trials in subjects with COPD. The incidence of adverse events in subjects taking non-potassium-sparing diuretics was similar between BEVESPI AEROSPHERE and placebo treatment groups. In addition, there was no evidence of a treatment effect on serum potassium with BEVESPI AEROSPHERE compared to placebo in subjects taking non-potassium-sparing diuretics during the two 24-week trials. However, caution is advised in the coadministration of BEVESPI AEROSPHERE with non-potassium-sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTC Prolonging Drugs

BEVESPI AEROSPHERE, as with other beta,-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or other 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 may be associated with an increased risk of ventricular arrhythmias.

7.5 Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and BEVESPI AEROSPHERE may interfere with the effect of each other when administered concurrently. Beta-blockers not only blunt the positive inotropic effects of beta,-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD 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 COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.6 Anticholinergics

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of BEVESPI AEROSPHERE with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see Warnings and Precautions (5.3, 5.10) and Adverse Reactions (6)].
Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta-agonists: seizures, angina, hypertension, hypotension, tachycardia, atrial and ventricular tachyarrhythmias, nervousness, headache, tremor, palpitations, muscle cramps, nausea, dizziness, sleep disturbances, metabolic acidosis, hyperglycemia, hypokalemia. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

11 DESCRIPTION

BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) Inhalation Aerosol is a pressurized metered-dose inhaler that contains a combination of micronized glycopyrrolate, an anticholinergic, and micronized formoterol fumarate, a long-acting beta2-adrenergic agonist, for oral inhalation.

Glycopyrrolate is a quaternary ammonium salt with the following chemical name: (R,S)-1-(5-Br-2-hydroxy-3-[(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl)phenyl formamide, €-2-butoximate dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is C19H28BrNO3, and the molecular weight is 398.33 g/mol. The structural formula is as follows:

Formoterol fumarate contains two chiral centers (denoted by * in structure above) and is a racemate of a 1:1 mixture of the R,S and S,R diastereomers. The active moiety, glycopyronium, is the positively charged ion of glycopyrrolate.

Formoterol fumarate has the chemical name 1H-[2,5-dihydroxy-5-[(1RS)-1-hydroxy-2-[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl formamide; €-2-butoximate dihydrate. Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is C19H28BrNO3, and the molecular weight is 398.33 g/mol. The structural formula is as follows:

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

BEVESPI AEROSPHERE is formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler containing 28 or 120 inhalations. The canister has an in-use volume of 40 mL. The actuator contains a fine mist or aerosol output of the drug in a propellant-free system. Each spray contains 100 mcg of glycopyrrolate and 110 mcg of formoterol fumarate from the valve which results in 8.3 mcg of glycopyrronium (glycopyrrolate) and 5.5 mcg of formoterol fumarate from the valve which results in 2.3 mcg of formoterol fumarate from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. BEVESPI AEROSPHERE also contains porous particles that form a cosuspension with the drug crystals. The porous particles and HFA 134a are excipients in the formulation.

Priming BEVESPI AEROSPHERE is essential to ensure appropriate drug content in each actuation. Prime BEVESPI AEROSPHERE before using for the first time. To prime BEVESPI AEROSPHERE, release 4 sprays into the air away from the face, shaking well before each spray.

If the product is not used for more than 7 days re-prime the device. To re-prime BEVESPI AEROSPHERE, release 2 sprays into the air away from the face, shaking well before each spray.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BEVESPI AEROSPHERE

BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate. The mechanism of action described below for the individual components apply to BEVESPI AEROSPHERE. These drugs represent two different classes of medications (a long-acting muscarinic antagonist and a long-acting selective beta2-adrenergic agonist) that have different effects on clinical and physiological indices.

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. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted more than 12 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

Formoterol Fumarate

Formoterol fumarate is a long-acting selective beta2-adrenergic agonist (beta2-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 has more than 200-fold greater agonist activity at beta2-receptors than at beta1-receptors. The in vitro binding selectivity to beta2 over beta1 adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) beta2-selectivity ratio than formoterol. Although beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta2-receptors are the predominant receptors in the heart, there are also beta1-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 beta2-agonists may have cardiac effects.

The pharmacologic effects of beta2-adrenergic agonist drugs, including formoterol fumarate, are at least in part attributable to stimulation of intracellular adenyl 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.

In vitro tests show that formoterol fumarate is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol fumarate also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

12.2 Pharmacodynamics

Cardiovascular effects: Healthy Subjects

The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% confidence bound) difference from placebo in baseline-corrected heart rate was 3.3 (4.9) beats/min and 7.6 (9.5) beats/min seen within 10 minutes of dosing with 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, respectively.

Chronic Obstructive Pulmonary Disease

The effect of glycopyrrolate/formoterol fumarate on cardiac rhythm in subjects with COPD was assessed using 24-hour Holter monitoring in 2-week and 24-week trials. All treatments were administered as two inhalations twice daily. In the 2-week trial, the Holter monitoring population included 58 subjects on glycopyrrolate/formoterol fumarate 18/4.8 mcg, 58 subjects on glycopyrrolate 18 mcg, and 60 subjects on formoterol fumarate 4.8 mcg. In the 24-week trial, the Holter monitoring population included 171 subjects on BEVESPI AEROSPHERE, 160 subjects on glycopyrrolate 9 mcg, 174 subjects on formoterol fumarate 4.8 mcg, and 80 subjects on placebo. No clinically meaningful effects on cardiac rhythm were observed.

12.3 Pharmacokinetics

Linear pharmacokinetics were observed for glycopyrrolate (dose range: 18 to 144 mcg) and formoterol fumarate (dose range: 2.4 to 19.2 mcg) after oral inhalation.

Absorption

Glycopyrrolate: Following inhaled administration of BEVESPI AEROSPHERE in subjects with COPD, Cmax occurred at 5 minutes. Steady state is expected to be achieved within 2-3 days of repeated dosing of BEVESPI AEROSPHERE and the extent of exposure is approximately 2.3 times higher than after the first dose.

Formoterol Fumarate: Following inhaled administration of BEVESPI AEROSPHERE in subjects with COPD, Cmax occurred within 20 to 60 minutes. Steady state is expected to be achieved within 2-3 days of repeated dosing with BEVESPI AEROSPHERE and the extent of exposure is approximately 1.5 times higher than after the first dose.

Distribution

Glycopyrrolate: Population pharmacokinetic analysis showed that estimated Vc/F (volume of the central compartment), and V2/F (volume of the peripheral compartment) are 951 L, and 209 L, respectively.

Formoterol Fumarate: Population pharmacokinetic analysis showed that estimated Vc/F (volume of the central compartment), and V2/F (volume of the peripheral compartment) are 951 L, and 209 L, respectively.

Metabolism

Glycopyrrolate: Based on information from the published literature, metabolism plays a minor role in the overall elimination of glycopyrrolate.

Formoterol Fumarate: The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include de-epoxidation and sulfitic conjugation. CVPD95 and CVPD2 have been identified as being primarily responsible for O-demethylation.

Elimination

Glycopyrrolate: After IV administration of a 0.2 mg radiolabeled glycopyrrolate, 85% of dose recovered was recovered in urine 48 hours post dose and some of radioactivity was also recovered in bile. The terminal elimination half-life derived via population pharmacokinetics analysis was 11.6 hours.

Formoterol Fumarate: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The terminal elimination half-life derived via population pharmacokinetics analysis was 11.8 hours.
Special Populations

Effect of age, sex, race/ethnicity, or body weight:
Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age, sex, race/ethnicity, or body weight on the pharmacokinetics of glycopyrrolate and formoterol.

Hepatic Impairment: Dedicated studies evaluating effect of hepatic impairment on the pharmacokinetics of glycopyrrolate and formoterol were not conducted.

Renal Impairment: Dedicated studies evaluating effect of renal impairment on the pharmacokinetics of glycopyrrolate and formoterol were not conducted. When glycopyrrolate was administered IV in uremic patients undergoing renal transplantation, mean elimination half-life was significantly longer (46.8 minutes) than in healthy patients (18.6 minutes). The mean AUC (10.6 hr·μg/L), mean plasma clearance (0.43 L/hr/kg), and mean 3-hour urine excretion (0.7%) for glycopyrrolate were also significantly different than those of controls (3.73 hr·μg/L, 1.14 L/hr/kg, and 50%, respectively). A population pharmacokinetic analysis using BEVESPI AEROSHERE showed that formoterol systemic exposure (AUC0-12) in subjects with COPD with moderate renal impairment (45 mL/min creatinine clearance) is expected to be approximately 45% higher compared to subjects with COPD with normal renal function (94 mL/min creatinine clearance).

Drug Interactions

No pharmacokinetic interaction is expected when glycopyrrolate and formoterol fumarate are administered in combination by the inhaled route. Specific drug-drug interaction studies have not been performed with glycopyrrolate or formoterol fumarate.

10 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BEVESPI AEROSHERE: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of BEVESPI AEROSHERE which contains glycopyrrolate and formoterol fumarate. The data described below for the individual components apply to BEVESPI AEROSHERE.

Glycopyrrolate

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of inhaled glycopyrrolate or any other formulations of glycopyrrolate. Glycopyrrolate was not mutagenic in the bacterial reverse mutation assay, the in vitro mammalian cell micronucleus assay in TK6 cells or the in vivo micronucleus assay in rats. In reproduction studies in rats, dietary administration of glycopyrrolate resulted in diminished rates of conception in a dose-related manner. Other studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

Formoterol Fumarate

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate. In a 24-month carcinogenicity study in CD-1 mice, formoterol fumarate at oral doses of 0.1 mg/kg and above (approximately 25 times the maximum recommended human daily inhalation dose (MRHDID) on a mg/m² basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 65 times the MRHDID on a mcg/m² basis). No tumors were seen at 22 mcg/kg (approximately 10 times the MRHDID on a mcg/m² basis). Other beta-agonist drugs have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown. Formoterol fumarate was not mutagenic or clastogenic in Ames Salmonella/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7600 times the MRHDID on a mg/m² basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7600 times the MRHDID on a mcg/m² basis), there were no changes in body weight, food consumption, clinical observations, hematology, or clinical chemistry. There was no evidence of a dose-related decrease in fertility or reproductive performance. The female rats were killed at the end of the study.

14 CLINICAL STUDIES

The safety and efficacy of BEVESPI AEROSHERE were evaluated in a clinical development program that included 8 dose-ranging trials and two placebo-controlled lung function trials of 24-weeks duration that included a 28-week extension study to evaluate safety over 1 year. The efficacy of BEVESPI AEROSHERE is based on the dose ranging trials in 822 subjects with COPD and the 2 placebo-controlled confirmatory trials in 3,705 subjects with COPD.

14.1 Dose-Ranging Trials

Dose selection for BEVESPI AEROSHERE for COPD was primarily based on data for the individual components, glycopyrrolate and formoterol fumarate, in COPD patients. Based on the findings from these studies, glycopyrrolate/formoterol fumarate 18/9.6 mcg administered twice-daily was evaluated in the confirmatory COPD trials.

Glycopyrrolate

Dose selection for glycopyrrolate was supported by a 14-day, randomized, double-blind, placebo-controlled, incomplete-block crossover trial evaluating 6 doses of glycopyrrolate (GM MDI 18 to 0.6 mcg) administered twice daily and an open-label active control in

14.2 Confirmatory Trials

The clinical development program for BEVESPI AEROSHERE included two (Trial 1 and Trial 2) 24-week, randomized, double-blind, placebo-controlled, parallel-group trials in subjects with moderate to severe COPD designed to evaluate the efficacy of BEVESPI AEROSHERE on lung function. The 24-week trials included 3,699 subjects that had a clinical diagnosis of COPD, were between 40 and 80 years of age, had a history of smoking greater than or equal to 10 pack-years, had a post-albuterol FEV1 less than 80% of predicted normal values, had a ratio of FEV1/FVC of less than 0.7. The majority of patients were male (58%) and Caucasian (91%) with a mean age of 63 years and an average smoking history of 51 pack-years (54% current smokers). During screening, mean post-bronchodilator percent predicted FEV1 was 51% (range: 19% to 82%) and mean percent reversibility was 20% (range: -32% to 135%).

Trial 1 and Trial 2 evaluated BEVESPI AEROSHERE (glycopyrrolate/formoterol fumarate) 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, and placebo administered twice daily (BID). Trial 1 also included an open-label active control. The primary endpoint was change from baseline in trough FEV1, at Week 24 compared with placebo, glycopyrrolate 18 mcg BID, and formoterol fumarate 9.6 mcg BID. The comparison of BEVESPI AEROSHERE with glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg was assessed to evaluate the contribution of the individual components to BEVESPI AEROSHERE. In both trials, BEVESPI AEROSHERE demonstrated a larger increase in mean change from baseline in trough FEV1, at Week 24 relative to placebo, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg (Table 2).
Table 2 – Least Square (LS) Mean Change from Baseline in Morning Pre-dose Trough FEV1 (mL) on Week 24 in Trial 1 and Trial 2 (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Placebo* LS Mean (95% CI)</th>
<th>Glycopyrrolate 18 mcg BID* LS Mean (95% CI)</th>
<th>Formoterol Fumarate 6 mcg BID* LS Mean (95% CI)</th>
<th>Difference from Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEVESPI AEROSPHERE</td>
<td>429</td>
<td>150 mL (114, 186)</td>
<td>N=344 (31, 68)</td>
<td>N=367 (36, 62)</td>
<td></td>
</tr>
<tr>
<td><strong>Trial 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEVESPI AEROSPHERE</td>
<td>433</td>
<td>103 mL (67, 140)</td>
<td>N=367 (25, 63)</td>
<td>N=350 (27, 65)</td>
<td></td>
</tr>
</tbody>
</table>

N = Number in the intent to treat population

*The placebo, glycopyrrolate and formoterol fumarate comparators used the same inhaler and excipients as BEVESPI AEROSPHERE.

With the limited data available, there were consistent improvements in trough FEV1, with respect to age, sex, degree of airflow limitation, GOLD stage, smoking status, or inhaled corticosteroid use.

In Trials 1 and 2, serial spirometric evaluations were performed throughout the 12-hour dosing interval in a subset of subjects (n=718 and n=595, respectively) at Day 1 and Week 12. Results from Trial 1 are shown in Figure 3. In Trial 2, the results for BEVESPI AEROSPHERE in FEV1; AUC0-12h were similar to those observed in Trial 1.

Figure 3 – Mean Change from Baseline in FEV1, over Time at Day 1 and Week 12 (Trial 1)

In both trials, peak FEV1 was defined as the maximum FEV1 recorded within 2 hours after the dose of trial medication. The mean peak FEV1 improvement from baseline with BEVESPI AEROSPHERE compared with placebo at Week 24 was 291 mL (95% CI: 252, 331) and 267 mL (95% CI: 226, 308) in Trial 1 and Trial 2, respectively. BEVESPI AEROSPHERE demonstrated an onset of bronchodilatory treatment effect at 5 minutes after the first dose based on a mean increase in FEV1 compared to placebo of 187 mL (95% CI: 168, 205) and 180 mL (95% CI: 164, 207) in Trial 1 and Trial 2, respectively. In both Trial 1 and 2, subjects treated with BEVESPI AEROSPHERE used less daily rescue albuterol compared to subjects treated with placebo.

The St. George’s Respiratory Questionnaire (SGRQ) was assessed in Trials 1 and 2. In Trial 1, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) was 37%, 30%, 35%, and 28% for BEVESPI AEROSPHERE, glycopyrrolate, formoterol fumarate, and placebo, respectively, with odds ratios of 1.2 (95% CI: 1.1, 1.8), 1.1 (95% CI: 0.9, 1.5), and 1.5 (95% CI: 1.1, 2.1), for BEVESPI AEROSPHERE vs. glycopyrrolate, BEVESPI AEROSPHERE vs. formoterol fumarate, and BEVESPI AEROSPHERE vs. placebo, respectively. In Trial 2, the trends were similar, with odds ratios of 1.2 (95% CI: 0.9, 1.6), 1.3 (95% CI: 1.0, 1.7), and 1.3 (95% CI: 0.9, 1.8), for BEVESPI AEROSPHERE vs. glycopyrrolate, BEVESPI AEROSPHERE vs. formoterol fumarate, and BEVESPI AEROSPHERE vs. placebo, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

BEVESPI AEROSPHERE Inhalation Aerosol is supplied as a pressurized aluminum canister with an attached dose indicator, a white plastic actuator and mouthpiece, and an orange dust cap. Each 120 inhalation canister has a net fill weight of 10.7 grams (NDC 0301-4600-12) and each 28 inhalation canister (institutional pack) has a net fill weight of 5.9 grams (NDC 0301-4600-29). Each canister is packaged in a foil pouch with desiccant sachet and is placed into an outer carton. Each carton contains one canister and a Patient Information leaflet.

The BEVESPI AEROSPHERE canister should only be used with the BEVESPI AEROSPHERE actuator, and the BEVESPI AEROSPHERE actuator should not be used with any other inhalation drug product.
PATIENT INFORMATION
BEVESPI AEROSPHERE™
(be-VES-pee AIR-oh-sfeer)
(glycopyrrolate and formoterol fumarate)
inhalation aerosol, for oral inhalation use

What is BEVESPI AEROSPHERE?
BEVESPI AEROSPHERE combines an anticholinergic, glycopyrrolate, and a long-acting beta2-adrenergic agonist (LABA) medicine, formoterol fumarate.

- Anticholinergic and LABA medicines 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.
- BEVESPI AEROSPHERE is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both.
- BEVESPI AEROSPHERE is used long term as 2 inhalations, 2 times each day in the morning and in the evening, to improve symptoms of COPD for better breathing.
- BEVESPI AEROSPHERE is not for use to treat sudden symptoms of COPD. Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat sudden symptoms. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- BEVESPI AEROSPHERE is not for the treatment of asthma. It is not known if BEVESPI AEROSPHERE is safe and effective in people with asthma.
- BEVESPI AEROSPHERE should not be used in children. It is not known if BEVESPI AEROSPHERE is safe and effective in children.

Do not use BEVESPI AEROSPHERE if you:
- are allergic to glycopyrrolate, formoterol fumarate, or to any of the ingredients in BEVESPI AEROSPHERE. See the end of this Patient Information leaflet for a complete list of ingredients.
- have asthma.

Before using BEVESPI AEROSPHERE, 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 eye problems such as glaucoma. BEVESPI AEROSPHERE may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. BEVESPI AEROSPHERE may make these problems worse.
- are allergic to any other medicines or food products
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if BEVESPI AEROSPHERE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicines, glycopyrrolate and formoterol fumarate, in BEVESPI AEROSPHERE pass into your breast milk and if they can harm your baby.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. BEVESPI AEROSPHERE and certain other medicines may interact with each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:
- anticholinergics (including tiotropium, ipratropium, aclidinium, and umecclidinium)
- other LABAs (including salmeterol, arformoterol, vilanterol, olodaterol, and indacaterol)
- atropine

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

How should I use BEVESPI AEROSPHERE?
Read the step-by-step instructions for using BEVESPI AEROSPHERE at the end of this Patient Information.

- Do not use BEVESPI AEROSPHERE unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Use BEVESPI AEROSPHERE exactly as prescribed. Do not use BEVESPI AEROSPHERE more often than prescribed.
- Use 2 inhalations of BEVESPI AEROSPHERE, 2 times each day (in the morning and in the evening).
- If you miss a dose of BEVESPI AEROSPHERE, take your next dose at the same time you normally do. Do not take more than your prescribed dose of BEVESPI AEROSPHERE.
- If you take too much BEVESPI AEROSPHERE, call your healthcare provider or go to the nearest hospital emergency room right away if you have unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- Do not spray BEVESPI AEROSPHERE in your eyes. If BEVESPI AEROSPHERE gets in your eyes, rinse them well with water. If redness continues, call your healthcare provider.
- Do not stop using BEVESPI AEROSPHERE unless told to do so by your healthcare provider because your symptoms might come back. Your healthcare provider will change your medicines as needed.
- 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 containing medicines.
- BEVESPI AEROSPHERE does not relieve sudden symptoms of COPD. 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, or your rescue inhaler does not work as well to relieve your symptoms.

What are the possible side effects with BEVESPI AEROSPHERE?
BEVESPI AEROSPHERE can cause serious side effects, including:

- people with asthma who take LABA medicines, such as formoterol fumarate (one of the medicines in BEVESPI AEROSPHERE), without also using a medicine called an inhaled corticosteroid, have an increased risk of serious problems from asthma, including being hospitalized, needing a tube placed in their airway to help them breathe, or death.
- Call your healthcare provider if breathing problems worsen over time while using BEVESPI AEROSPHERE. You may need a different treatment.
- Get emergency medical care if:
  - your breathing problems worsen quickly
  - you use your rescue inhaler medicine, but it does not relieve your breathing problems
- using too much of a LABA medicine may cause:
  - chest pain
  - increased blood pressure
  - fast and irregular heartbeat
  - headache
  - tremor
  - nervousness
- COPD symptoms can get worse over time. If your COPD symptoms worsen over time, do not increase your dose of BEVESPI AEROSPHERE, instead call your healthcare provider.
- sudden breathing problems immediately after inhaling your medicine. If you have sudden breathing problems immediately after inhaling your medicine, stop using BEVESPI AEROSPHERE 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
  - swelling of the face, mouth, and tongue
  - hives
  - breathing problems
- effects on your heart:
  - increase blood pressure
  - chest pain
  - a fast or irregular heartbeat
- effects on your nervous system:
  - tremor
  - nervousness
- changes in laboratory blood levels, including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia) which may cause symptoms of muscle spasm, muscle weakness or abnormal heart rhythm.
- new or worsened eye problems including acute narrow-angle glaucoma. 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
  - seeing halos or bright colors around lights
  - nausea or vomiting
  - red eyes
  - blurred vision
If you have these symptoms, call your healthcare provider right away before taking another dose.
- urinary retention. People who take BEVESPI AEROSPHERE may develop new or worse urinary retention. Symptoms of urinary retention may include:
  - difficulty urinating
  - urinating frequently
  - painful urination
  - urination in a weak stream or drips
If you have these symptoms of urinary retention, stop taking BEVESPI AEROSPHERE and call your healthcare provider right away before taking another dose.

Common side effects of BEVESPI AEROSPHERE include: urinary tract infection and cough.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of BEVESPI AEROSPHERE. For more information, ask your healthcare provider or pharmacist. 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 AstraZeneca at 1-800-236-9933.

How should I store BEVESPI AEROSPHERE?
- Store BEVESPI AEROSPHERE at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not put a hole in the BEVESPI AEROSPHERE canister.
- Do not use or store BEVESPI AEROSPHERE near heat or a flame. Temperatures above 120°F (49°C) may cause the canister to burst.
- Do not throw the BEVESPI AEROSPHERE canister into a fire or an incinerator.
- Throw away BEVESPI AEROSPHERE 3 months after you open the foil pouch (3 weeks for the 28 inhalation canister) or when the dose indicator reaches zero “0”, whichever comes first.
- Keep BEVESPI AEROSPHERE and all medicines out of the reach of children.

General Information about the safe and effective use of BEVESPI AEROSPHERE
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BEVESPI AEROSPHERE for a condition for which it was not prescribed. Do not give your BEVESPI AEROSPHERE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about BEVESPI AEROSPHERE that is written for health professionals.

Active ingredients: micronized glycopyrrolate and micronized formoterol fumarate
Inactive ingredients: hydrofluoroalkane (HFA 134a) and porous particles (comprised of DSPC [1,2-Distearoyl-sn-glycero-3-phosphocholine] and calcium chloride)
Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
©AstraZeneca 2019
For more information, call 1-800-236-9933 or go to www.BEVESPI.com.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: May 2019 US-25519 6/19
Instructions for Use
BEVESPI AEROSPHERE™
(be-VES-pee AIR-oh-sfeer)
glycopyrrolate and formoterol fumarate)
Inhalation aerosol, for oral inhalation use

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

Important Information:
• For oral inhalation use only.
• Use BEVESPI AEROSPHERE exactly as your healthcare provider tells you to.
• If you have any questions about the use of your inhaler, ask your healthcare provider or pharmacist.

Parts of your BEVESPI AEROSPHERE inhaler (See Figure 1):
• BEVESPI AEROSPHERE comes as a canister that fits into an actuator with a dose indicator.
  ° Do not use the BEVESPI AEROSPHERE actuator with a canister of medicine from any other inhaler.
  ° Do not use the BEVESPI AEROSPHERE canister with an actuator from any other inhaler.

BEVESPI AEROSPHERE comes with a dose indicator located on the top of the canister (See Figure 1). The dose indicator display window will show you how many puffs of medicine you have left. A puff of medicine is released each time you press the center of the dose indicator.

Before you use BEVESPI AEROSPHERE for the first time make sure that the pointer on the dose indicator is pointing to the right of the “120” inhalation mark in the dose indicator display window (See Figure 1). (Note, the pointer will point to the right of the “30” inhalation mark if you have a 7-day inhaler, 28 inhalation canister.)
• The pointer will be pointing to 120 after 10 puffs are delivered from BEVESPI AEROSPHERE. This means that there are 120 puffs of medicine left in the canister (See Figure 2a).
• The pointer will be pointing between 100 and 120 after you take 10 more puffs. This means that there are 110 puffs of medicine left in the canister (See Figure 2b).

Before you use BEVESPI AEROSPHERE make sure the pointer on the dose indicator is pointing to the right of the “120” inhalation mark in the dose indicator display window (See Figure 1). (Note, the pointer will point to the right of the “30” inhalation mark if you have a 7-day inhaler, 28 inhalation canister.)
• The color in the dose indicator display window will change to red, as shown in the shaded area, when there are only 20 puffs of medicine left in your inhaler (See Figure 2d).
• The dose indicator for the 7-day inhaler, 28 inhalation canister, moves after every 10 puffs; with markings for 30, 15 and 0 puffs. The color in the 7-day inhaler, 28 inhalation canister, dose indicator display window will change to red when there are only 10 puffs of medicine left in your inhaler.

Preparing your BEVESPI AEROSPHERE inhaler for use:
• BEVESPI AEROSPHERE should be at room temperature before you use it.
• Your BEVESPI AEROSPHERE inhaler comes in a foil pouch that contains a drying packet (desiccant).
  ° Take the BEVESPI AEROSPHERE inhaler out of the foil pouch.
  ° Throw away the pouch and the drying packet. Do not eat or breathe in the contents of the drying packet.
Priming your BEVESPI AEROSPHERE inhaler:
Before you use BEVESPI AEROSPHERE for the first time, you must prime the inhaler.
• Remove the cap from the mouthpiece (See Figure 3). Check inside the mouthpiece for objects before use.
• Hold the inhaler in the upright position away from your face and shake the inhaler well (See Figure 4).

• Press down firmly on the center of the dose indicator until the canister stops moving in the actuator, to release a puff of medicine from the mouthpiece (See Figure 5). You may hear a soft click from the dose indicator as it counts down during use.

• Repeat the priming steps 3 more times (See Figure 4 and Figure 5). Shake the inhaler well before each priming puff.
• After priming 4 times, the dose indicator should be pointing to the right of “120” and your inhaler is now ready to use.

Using your BEVESPI AEROSPHERE inhaler:
Step 1: Remove the cap from the mouthpiece (See Figure 6).
Step 2: Shake the inhaler well before each use (See Figure 7).
Step 3: Hold the inhaler with the mouthpiece pointing towards you and breathe out as fully as you comfortably can through your mouth (See Figure 8).
Step 4: Close your lips around the mouthpiece and tilt your head back, keeping your tongue below the mouthpiece (See Figure 9).
Step 5: While breathing in deeply and slowly, press down on the center of the dose indicator until the canister stops moving in the actuator and a puff of medicine has been released (See Figure 10). Then stop pressing the dose indicator.
Step 6: When you have finished breathing in, remove the mouthpiece from your mouth. Hold your breath as long as you comfortably can, up to 10 seconds (See Figure 11).
Step 7: Breathe out gently (See Figure 12). Repeat steps 2 through 7 to take your second puff of BEVESPI AEROSPHERE.

Step 8: Replace the cap over the mouthpiece right away after use (See Figure 13).

How to clean your BEVESPI AEROSPHERE inhaler:
Clean the inhaler 1 time each week. It is very important to keep your inhaler clean so that medicine will not build-up and block the spray through the mouthpiece (See Figure 14).

Step 1: Take the canister out of the actuator (See Figure 15). Do not clean the canister or let it get wet.

Step 2: Take the cap off the mouthpiece.
Step 3: Hold the actuator under the faucet and run warm water through it for about 30 seconds. Turn the actuator upside down and rinse the actuator again through the mouthpiece for about 30 seconds (See Figure 16).

Step 4: Shake off as much water from the actuator as you can.
Step 5: Look into the actuator and the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Steps 3 through 5 in the section “How to clean your BEVESPI AEROSPHERE inhaler”.
Step 6: Let the actuator air-dry overnight (See Figure 17). Do not put the canister back into the actuator if it is still wet.
Step 7: When the actuator is dry, gently press the canister down in the actuator (See Figure 18). Do not press down too hard on the canister. This could cause a puff of medicine to be released.

Step 8: Re-prime your BEVESPI AEROSPHERE inhaler after each cleaning. To re-prime the inhaler, shake the inhaler well and press down on the center of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

If you do not use your BEVESPI AEROSPHERE for more than 7 days, you will need to re-prime it before use.

To re-prime the inhaler, shake the inhaler well and press down on the center of the dose indicator 2 times to release a total of 2 puffs into the air away from your face. Your inhaler is now ready to use.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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