



Glycopyrrolate and formoterol (Bevespi Aerosphere™) New Drug Update

May 2016

Drug Name:	glycopyrrolate and formoterol
Trade Name (Manufacturer):	Bevespi Aerosphere (AstraZeneca)
Form:	Inhalation aerosol (pressurized metered dose inhaler)
Strength:	9 mcg/4.8 mcg per inhalation
FDA Approval:	April 26, 2016
Market Availability:	TBD
FDA Approval Classification:	N/A
Classification:	Specific Therapeutic Class (HIC3): Beta-adrenergic and anticholinergic combo, inhaled (B62)

INDICATION¹

Glycopyrrolate and formoterol (Bevespi Aerosphere) is indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Glycopyrrolate and formoterol is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

PHARMACOKINETICS

Following inhaled administration of the medication in patients with COPD, peak serum concentration (C_{max}) occurred in 5 minutes and 20 to 60 minutes with glycopyrrolate and formoterol, respectively. Steady state is expected within 2 to 3 days of repeated dosing. Elimination occurs primarily in the urine (85% for glycopyrrolate and 62% for formoterol). Glycopyrrolate also undergoes excretion via bile and 24% of formoterol is eliminated through feces. The elimination half-life of glycopyrrolate/formoterol is 11.8 hours.

CONTRAINDICATIONS/WARNINGS

All long-acting beta agonists (LABAs) are contraindicated in patients with asthma without the use of a long-term asthma control medication. Glycopyrrolate/formoterol is not indicated for asthma. Patients with a hypersensitivity to glycopyrrolate, formoterol, or any component of the product should not use glycopyrrolate/formoterol.

LABAs may increase the risk of asthma-related death (black box warning); however, data are not available to determine whether the rate of death in patients with COPD is increased.

Glycopyrrolate/formoterol should not be started in patients with acutely deteriorating COPD and has not been studied in this population. Glycopyrrolate/formoterol should not be used for relief of acute symptoms. Patients using a short-acting beta₂-agonist on a regular basis should be instructed to discontinue its regular use and use only when symptomatic when starting glycopyrrolate/formoterol therapy. Patients should have access to a short-acting beta₂-agonist and monitor use as an increase in use could indicate deteriorating disease.

Cardiovascular effects and fatalities have been reported in association with overuse of inhaled sympathomimetic medications. Other LABAs should not be used when using glycopyrrolate/formoterol.

As with other inhaled medications, glycopyrrolate/formoterol can produce paradoxical bronchospasm which could be life threatening.

Hypersensitivity reactions have occurred with glycopyrrolate/formoterol.

Like other beta₂-agonists, formoterol can produce increases in pulse rate, systolic or diastolic blood pressure, and other cardiovascular symptoms. Beta₂-agonists have also been reported to cause electrocardiographic changes, hypokalemia, and hyperglycemia; use cautiously.

Glycopyrrolate/formoterol should be used with caution in patients with convulsive disorders, thyrotoxicosis, narrow-angle glaucoma, or urinary retention or in those who are unusually responsive to sympathomimetic amines.

DRUG INTERACTIONS

No formal drug interaction studies have been performed.

If used with adrenergic medications, the sympathetic effects of formoterol may be potentiated. Concurrent use of formoterol and xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effects. QTc interval prolongations may occur with the use of beta₂-agonists and monoamine oxidase inhibitors or tricyclic antidepressants. Beta-blockers may block the therapeutic effects of beta₂-agonists and produce severe bronchospasm in COPD patients. The use of anticholinergics should be avoided due to additive effects.

COMMON ADVERSE EFFECTS

The most common adverse reactions with ≥ 2% incidence and more common than with placebo include cough (4%) and urinary tract infection (2.6%). Other adverse reactions with an incidence of < 2% but more common than with placebo include: acute sinusitis, anxiety, arthralgia, chest pain, contusion, dizziness, dry mouth, extremity pain, fall, fatigue, headache, influenza, muscle spasm, oropharyngeal pain, tooth abscess, and vomiting.

SPECIAL POPULATIONS

Pregnancy

Pregnancy Category C.

Pediatrics

Safety and efficacy has not been established; glycopyrrolate/formoterol is not indicated for use in children.

Geriatrics

There is no need for dose adjustment in geriatric patients but older patients may have greater sensitivity.

Hepatic Impairment

No formal studies have been conducted. However, formoterol is primarily cleared by hepatic metabolism and impairment may lead to accumulation of formoterol. Monitoring is recommended.

Renal Impairment

No formal studies have been conducted. In patients with severe renal impairment (creatinine clearance ≤ 30 mL/min/1.73 m²) or end-stage renal disease requiring dialysis, glycopyrrolate/formoterol should be used only when benefits outweigh the risk.

DOSAGES

Glycopyrrolate/formoterol 9 mcg/4.8 mcg should be taken as 2 oral inhalations twice daily in the morning and in the evening. Do not exceed 2 inhalations twice daily.

There are 120 inhalations per container which has an indicator showing how many inhalations are remaining. When nearing the end of usable inhalations the color behind the number in the display window will turn red. When the dose indicator is zero the inhaler should be discarded or 3 months after removal from the foil pouch, whichever comes first. The correct amount of medication in each inhalation cannot be assured after the indicator shows zero, even though the canister may not feel empty.

Glycopyrrolate/formoterol should be primed before first use and if not used for more than 7 days. When priming for the first time the user should shake well before each spray and release 4 sprays into the air. To re-prime, the user should shake well before each spray and release 2 sprays into the air.

CLINICAL TRIALS²

A literature search was performed using “formoterol” and “glycopyrrolate”.

The safety and efficacy of glycopyrrolate/formoterol (Bevespi Aerosphere) were assessed in 8 dose-ranging trials, 2 placebo-controlled lung function trials of 24 weeks, and a 28 week extension study to evaluate safety over 1 year.

Dosing ranging studies were primarily based on data for the individual components of the drug in COPD patients. Dose ranging glycopyrrolate trials in patients with COPD demonstrated minimal additional benefit at doses above 18 mcg twice daily. Formoterol 9.6 mcg showed larger improvements in FEV₁ in dose-ranging trials over 12 hours compared to the lower doses. Based on findings from these studies, glycopyrrolate/formoterol 18 mcg/9.6 mcg twice daily was evaluated in the confirmatory COPD trials.

Two (Trial 1 and Trial 2), 24-week, randomized, double-blind, placebo-controlled, parallel-group confirmatory trials were conducted in patients with moderate to very severe COPD (n=3,699; ages 40 to 80 years old; history of smoking ≥ 10 pack-years; post-albuterol forced expiratory volume in 1 second [FEV₁] < 80% of predicted normal values; FEV₁/forced vital capacity [FVC] ratio < 0.7). Trial 1 and Trial 2 evaluated glycopyrrolate/formoterol 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol 9.6 mcg, and placebo twice daily. Trial 1 also had an open-label active control. In both trials glycopyrrolate/formoterol showed a larger increase in mean change from baseline in trough FEV₁ at Week 24 compared to placebo (150 mL [95% confidence interval (CI), 114 to 186] and 103 mL [95% CI, 67 to 140] in Trials 1 and 2, respectively), glycopyrrolate (59 mL [95% CI, 31 to 88] and 54 mL [95% CI, 25 to 83], respectively), and formoterol (64 mL [95% CI, 36 to 92] and 56 mL [95% CI, 27 to 85], respectively), the primary endpoint. In Trial 1 and Trial 2, the mean peak FEV₁ improvement from baseline compared to placebo at Week 24 was 291 mL (95% CI, 252 to 331) and 267 mL (95% CI, 226 to 308) in Trials 1 and 2, respectively. Glycopyrrolate/formoterol also showed an onset of bronchodilatory effect at 5 minutes after the first dose based on a mean increase in FEV₁ compared to placebo in both trials. In Trial 1, the St. George's Respiratory Questionnaire (SGRQ) responder rate (defined as an improvement in score of ≥ 4) was 37%, 30%, 35%, and 28% for glycopyrrolate/formoterol, glycopyrrolate, formoterol, and placebo, respectively, with odds ratios of 1.4 (95% CI, 1.1 to 1.8), 1.1 (95% CI, 0.9 to 1.5), and 1.5 (95% CI, 1.1 to 2.1) for glycopyrrolate/formoterol versus glycopyrrolate, glycopyrrolate/formoterol versus formoterol, and glycopyrrolate/formoterol versus placebo, respectively. Trends were similar in Trial 2 with odds ratios of 1.2 (95% CI, 0.9 to 1.6), 1.3 (95% CI, 1.0 to 1.7), and 1.3 (95% CI, 1.0 to 1.8) for glycopyrrolate/formoterol versus glycopyrrolate, glycopyrrolate/formoterol versus formoterol, and glycopyrrolate/formoterol versus placebo, respectively. Consistent improvements were also observed in trough FEV₁ with respect to age, sex, degree of airflow limitation, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, smoking status, and inhaled corticosteroid. Decreased use of daily rescue albuterol with glycopyrrolate/formoterol was observed in both trials compared to placebo.

OTHER DRUGS USED FOR CONDITION³

There are several medications in the market place for the treatment of COPD including acclidinium bromide inhalation powder (Tudorza[®] Pressair[®]), albuterol/ipratropium inhalation solution, albuterol/ipratropium metered dose inhaler (MDI) (Combivent[®] Respimat[®]), glycopyrrolate (Seebri[™] Neohaler[®]), ipratropium inhalation solution, ipratropium inhalation aerosol MDI (Atrovent[®] HFA), roflumilast (Daliresp[®]), tiotropium dry powder inhaler (DPI; Spiriva HandiHaler[®]), tiotropium bromide inhalation spray (Spiriva[®] Respimat[®]), and umeclidinium inhalation powder (Incruse[®] Ellipta[®]). Three other LABA/anticholinergic oral inhalers for the treatment of COPD include: indacaterol/glycopyrrolate (Utibron[™] Neohaler[®]), tiotropium/olodaterol (Stiolto[™] Respimat[®]), and umeclidinium/vilanterol DPI (Anoro[®] Ellipta[®]).

PLACE IN THERAPY⁴

The 2016 updated GOLD Global Strategy for the Diagnosis, Management, and Prevention of COPD guidelines' Classification of Airflow Limitation utilizes post-bronchodilator FEV₁ to classify severity, which is divided into 4 Grades. Patients are then grouped into 4 categories using this GOLD Grade, exacerbation history, and symptom scores: Group A (low risk, less symptoms), Group B (low risk, more symptoms), Group C (high risk, less symptoms), and Group D (high risk, more symptoms).

The 2016 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories. The combination of a long-acting beta₂-agonist and a long-acting anticholinergic, such as glycopyrrolate/formoterol, is recommended for patients in Groups C and D as a primary therapy, and it may be considered as an alternative in Group B patients. Single agents (long-acting beta₂-agonists or anticholinergics) are generally recommended for patients with lower risks, but may also be used in higher risk patients as an alternative to combination therapy. Other alternatives for these high-risk patients include use of a phosphodiesterase-4 (PDE4) and the addition of an inhaled corticosteroid.

Glycopyrrolate/formoterol offers an additional long-acting anticholinergic/beta₂-agonist formulation.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	COPD Agents
Clinical Edit	<p>Prior authorization will be required if product is determined to be non-preferred. Patient must:</p> <ul style="list-style-type: none"> ▪ be 18 years old or older; AND ▪ have a diagnosis of COPD; AND ▪ have rescue therapy on file. <p>The patient must NOT:</p> <ul style="list-style-type: none"> ▪ be using the medication for asthma; OR ▪ have acutely deteriorating COPD; OR ▪ be using the medication for relief of acute symptoms; OR ▪ be using other LABAs; OR ▪ be using other long-acting anticholinergic agents.
Quantity Limit	1 canister/30 days
Duration of Approval	1 year
Drug to Disease Hard Edit	Asthma

REFERENCES

1 Bevespi Aerosphere [package insert]. Wilmington, DE; AstraZeneca; April 2016.

2 Bevespi Aerosphere [package insert]. Wilmington, DE; AstraZeneca; April 2016.

3 Available at: <http://www.clinicalpharmacology.com/>. Accessed May 10, 2016.

4 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Updated 2016. Available at: <http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/>. Accessed May 10, 2016.