Drug Monograph

Drug/Drug Class:	**Bevespi Aerosphere® (glycopyrrolate and formoterol fumarate) aerosol/ COPD Agents**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Bevespi Aerosphere® is a pressurized metered dose inhaler that delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate per inhalation. Manufacturer: AstraZeneca Pharmaceuticals LP, Wilmington, DE 49850
Summary of Findings:	Bevespi Aerosphere® was evaluated in 2 randomized, double-blind, placebo-controlled, parallel-group, 24 week trials in patients with moderate to severe COPD. In both studies, Bevespi Aerosphere® demonstrated a mean peak FEV_1 improvement from baseline compared with placebo. Also, Bevespi Aerosphere® demonstrated an onset of bronchodilatory treatment effect at 5 minutes after the first dose based on a mean increase in FEV_1 when compared with placebo. The St. George's Respiratory Questionnaire 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. Patients treated with Bevespi Aerosphere® used less daily rescue albuterol compared to subjects treated with other agents.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, is a chronic lung disease that makes it hard to breathe. The disease is increasingly common, affecting millions of Americans, and is the third leading cause of death in the U.S. COPD is often preventable and treatable.

Dosage Form(s) [1]

Bevespi Aerosphere® is a pressurized metered dose inhaler that delivers 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate per inhalation.

Manufacturer [1]

AstraZeneca Pharmaceuticals LP, Wilmington, DE 49850

Indication(s) [1]

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

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Bevespi Aerosphere® contains both glycopyrrolate and formoterol fumarate. Glycopyrrolate is a long acting anticholinergic agent. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. Formoterol fumarate is a long acting selective beta$_2$-adrenergic agonist with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator.

Pharmacokinetics:

	Glycopyrrolate	**Formoterol**
Steady State Reached	2-3 days of repeated dosing	2-3 days of repeated dosing
Volume of Distribution	Central – 951 L Peripheral – 2019 L	Central – 948 L Peripheral – 434 L

Treatment with Bevespi Aerosphere® resulted in a larger increase in mean change from baseline in trough FEV_1 at Week 24 when compared to placebo, glycopyrrolate 18 mcg, and formoterol fumarate 9.6 mcg.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, parallel-group, 24 week trial.
INCLUSION CRITERIA	Adults with 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 FEV_1 less than 80% of predicted normal values, and had a ratio of FEV_1/FVC of less than 0.7.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive either Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate) 18 mcg/9.6 mcg, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo administered twice daily.
RESULTS	The mean peak FEV_1 improvement from baseline with Bevespi Aerosphere® compared with placebo at Week 24 was 291 ml. Bevespi Aerosphere® demonstrated an onset of bronchodilatory treatment effect at 5 minutes after the first dose based on a mean increase in FEV_1 compared to placebo of 187 ml. The St. George's Respiratory Questionnaire (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. Subjects treated with Bevespi Aerosphere® used less daily rescue albuterol compared to subjects treated with placebo.
SAFETY	Not specified.

Contraindications [(1)]

- Hypersensitivity to glycopyrrolate, formoterol, or any component of the formulation
- As monotherapy in patients with asthma

Warnings and Precautions [(1)]

- Long acting $beta_2$-agonists increase the risk of asthma-related death.
- Do not use for acute episodes of COPD or for acute bronchospasm; always prescribe with an inhaled short-acting $beta_2$-agonist and educate patient on appropriate use.
- Rarely, paradoxical, life-threatening bronchospasm may occur with use of inhaled $beta_2$-agonists; distinguish between inadequate response and discontinue medication immediately if paradoxical bronchospasm occurs
- Use with caution in patients with cardiovascular disease; beta-agonists may cause elevation in blood pressure and heart rate.
- Use with caution in patients with seizure disorders; $beta_2$-agonists may result in CNS stimulation/excitation.
- Use with caution in patients with diabetes mellitus; $betra_2$-agonists may aggravate preexisting diabetes and ketoacidosis and increase serum glucose.

- Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.
- Use with caution in patients with narrow angle glaucoma; monitor of signs/symptoms of glaucoma.
- Use with caution in patients with urinary retention.
- Use with caution in patients with hyperthyroidism; may stimulate thyroid activity.
- Immediate hypersensitivity reactions have been reported; if signs suggesting allergic reactions occur, discontinue therapy immediately.
- Use with caution in patients with severe renal impairment or end stage renal disease on dialysis.
- Use with caution in patients with hepatic function impairment.
- My cause drowsiness, dizziness, and/or blurred vision.

Adverse Effects [(1)]

Most common, ≥ 2 %	Bevespi Aerosphere® (n=1036)	Glycopyrrolate 18 mcg BID (n=890)	Formoterol Fumarate 9.6 mcg BID (n=890)	Placebo (n=443)
Cough	4%	3%	2.7%	2.7%
Urinary Tract Infection	2.6%	1.8%	1.5%	2.3%

Drug Interactions [(1)]

- Adrenergic Drugs
- Xanthine derivatives, steroids, or diuretics
- Non-potassium sparing diuretics
- Monoamine oxidase inhibitors, tricyclic antidepressants, QTc Prolonging Drugs
- Beta-blockers
- Anticholinergics

Dosage and Administration [(1)]

Bevespi Aerosphere® should be administered as two inhalations take twice daily in the morning and in the evening by the orally inhaled route only. Do not take more than two inhalations twice daily.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ MONTH*
Glycopyrrolate /Formoterol Fumarate	Bevespi Aerosphere	AstraZeneca	9 mcg/4.8 mcg	2 inhalations twice daily	$315.65
Indacaterol/ glycopyrrolate	Utibron Neohaler	Novartis	27.5 mcg/15.6	1 capsule twice daily	$297.60

			mcg capsules		
Umeclidinium/ Vilanterol	Anoro Ellipta	GlaxoSmithKline	62.5 mcg/25 mcg blisters	Once daily	$315.60

* Wholesale Acquisition Cost

Conclusion

Bevespi Aerosphere® is a combination of an anticholinergic agent, glycopyrrolate, and a long acting beta$_2$-agonist, formoterol fumarate. Bevespi Aerosphere® was studied in two 24 week, randomized, double-blind, placebo-controlled, parallel-group, lung function trials in patients with moderate to very severe COPD. Patients were randomized to receive Bevespi Aerosphere®, glycopyrrolate 18 mcg, formoterol fumarate 9.6 mcg, or placebo twice daily. Patients using Bevespi Aerosphere® were found to have a statistically significant improvement in morning predose trough FEV_1 compared with glycopyrrolate, formoterol fumarate, or placebo. The Bevespi Aerosphere® group also demonstrated a significant improvement, compared with placebo, in peak FEV_1 within 2 hours after medication administration and rescue medication use.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1. Bevespi Aerosphere. Retrieved 11/25/2016 from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ae02436e-9528-490e-a844-0c0f6f2843f9
2. Hamburg, Monica. Bevespi Aerosphere. Retrieved 11/25/2016 from http://www.pharmacytimes.com/publications/issue/2016/september2016/bevespi-aerosphere

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