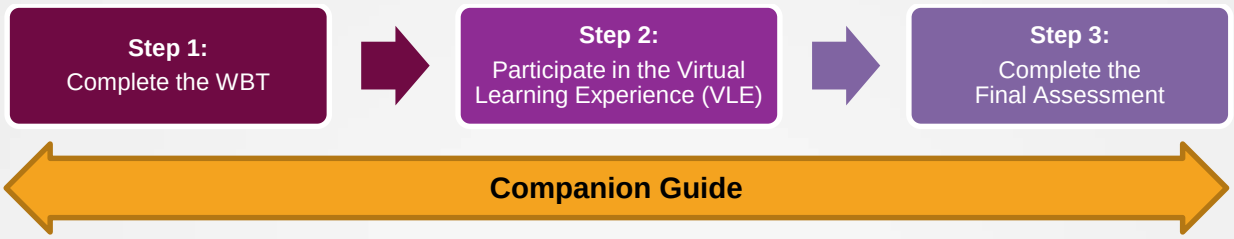
Purpose

This Companion Guide is designed as a companion piece to the BEVESPI AEROSPHERE™ Annotated PI web-based training (WBT). It provides an overview of the key concepts from the WBT and areas to take notes. It also includes a few "Thought Questions," for you to answer, providing you an opportunity to begin to apply what you have learned, and prepare you for the corresponding virtual learning experience (VLE). A completed Companion Guide can be used to help prepare you to take the final assessment. The Guide concludes with "Reflective Questions" designed to help you think more deeply about the content in this module and how to apply it in a real-world setting.



How to Use This Companion Guide

This guide includes the following sections:

- Introduction
- Module Print Summary interspersed with space for creating your own notes and Thought Questions to reinforce what you have learned
- Reflective Questions

You may have chosen to print this Companion Guide either before or after completion of the corresponding WBT.

Using it *BEFORE* Completing the WBT:

If you have chosen to print this Companion Guide prior to reviewing the WBT, you can take notes within the Print Summary while reviewing it. We recommend waiting to complete the Thought and Reflective Questions until after WBT completion, see below.

Using it *AFTER* Completing the WBT:

If you have chosen to print it after WBT completion, then review the Print Summary and notes sections to refresh on the key concepts in preparation for the corresponding VLE and answer the Thought Questions. Then during the VLE, take additional notes on your printed Companion Guide to further solidify key concepts.

Answering the Questions

After completing the WBT, answer the Reflective Questions as a way to apply what you have learned and to prepare you to be an active participant in the VLE.

You can then re-review the Print Summary and answers to the questions in preparation for taking the final assessment.

Module: BEVESPI AEROSPHERE™ (glycopyrrolate/formoterol fumarate): Annotated Prescribing Information Print Summary

Boxed Warning

Learning Objective:

- Explain the contents of the boxed warning

Boxed Warning

WARNING: ASTHMA-RELATED DEATH

See full Prescribing Information (PI) for complete boxed warning:

- Long-acting beta$_2$-adrenergic agonists (LABAs), such as formoterol fumarate, one of the active ingredients in BEVESPI AEROSPHERE, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including formoterol fumarate.

- 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.

Indications and Usage

Learning Objective:

- State the approved indications for BEVESPI AEROSPHERE

Indication

BEVESPI AEROSPHERE is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.

Important Limitation of Use

The safety and efficacy of BEVESPI AEROSPHERE in patients with asthma have not been established. Therefore, under Important Limitations of Use in the P, it states that BEVESPI AEROSPHERE is not indicated for the treatment of asthma.

Dosage and Administration

Learning Objective:

- Describe how BEVESPI AEROSPHERE is dosed and administered

Dosage

- BEVESPI AEROSPHERE (glycopyrrolate/9 mcg* and formoterol fumarate/4.8 mcg) is administered as 2 oral inhalations twice daily (BID; morning and evening)
- No more than 2 inhalations BID should be taken

*NOTE: You may see micrograms abbreviated as “mcg” or as “µg”.

Priming

- Priming BEVESPI AEROSPHERE is essential to ensure the appropriate drug content in each actuation
- Prime BEVESPI AEROSPHERE before using for the first time. To prime, release 4 sprays into the air away 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, release 2 sprays into the air away from the face, shaking well before each spray

Dosage Form and Strength

Learning Objective:

- Identify the available dosage form and strength for BEVESPI AEROSPHERE

Dosage Form and Strength

- Per inhalation, BEVESPI AEROSPHERE pressurized metered-dose inhaler (pMDI) delivers of 9 mcg of glycopyrrolate and 4.8 mcg of formoterol fumarate
- 2 inhalations = 1 dose
- Each canister contains 120 inhalations and is supplied with a white plastic actuator and orange dust cap

Fixed Dosing:

BEVESPI AEROSPHERE is a fixed-dose pMDI with only 1 dosage strength. When used as indicated, 120 inhalations corresponds to a 30-day supply of treatment.

Contraindications

Learning Objective:

- Identify the contraindications to the use of BEVESPI AEROSPHERE

Contraindications

All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. 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.

Warnings and Precautions

Learning Objective:

- Describe the warnings and precautions for BEVESPI AEROSPHERE

Warnings and Precautions

List the 10 warnings and precautions included in the BEVESPI AEROSPHERE PI and take any additional notes to help you remember key details describing each warning or precaution.

	Warning or Precaution	Notes
1		
2		

	Warning or Precaution	Notes
3		
4		
5		
6		
7		
8		
9		
10		

Adverse Reactions

Learning Objective:

- State the adverse reactions that may be associated with BEVESPI AEROSPHERE

Most Common Adverse Reactions

QUESTION: In Trials 1 and 2, which adverse reactions occurred in ≥2% of patients with COPD and were more common in patients treated with BEVESPI AEROSPHERE than with placebo?

1. _____

2. _____

Additional Adverse Reactions

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, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

_____

_____

_____

Long-Term Safety Extension Trial

The PI also includes data from a long-term safety extension trial. In this study, 893 patients who successfully completed Trial 1 or Trial 2 were treated for up to an additional 28 weeks, for a total treatment period of up to 52 weeks. The adverse reactions reported in the long-term safety trial were consistent with those observed in the 24-week placebo-controlled trials.

_____

_____

_____

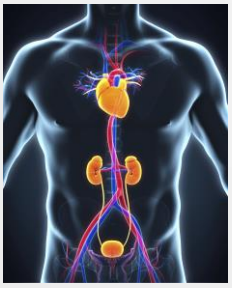
Drug Interactions

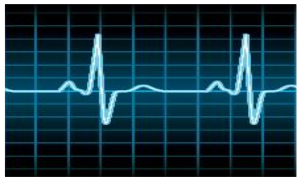
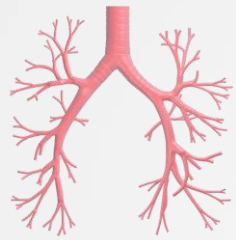
Learning Objective:

- State the drug interactions that may be associated with BEVESPI AEROSPHERE

Drug Interactions

The BEVESPI AEROSPHERE PI lists the following possible drug interactions. Use the space provided below for taking your own notes to help you remember the key points that are most relevant to your particular needs.

Drug Interaction	Additional Notes
Adrenergic drugs 	
Xanthine derivatives, steroids, or diuretics 	
Non–potassium-sparing diuretics 	

Drug Interaction	Additional Notes
Monoamine oxidase inhibitors, tricyclic antidepressants, QTc-prolonging drugs 	
Beta-blockers 	
Anticholinergics 	

Use in Specific Populations

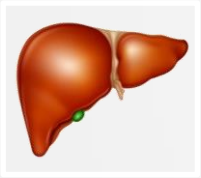
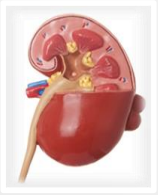
Learning Objective:

- Describe the use of BEVESPI AEROSPHERE in specific populations

Use in Specific Populations

The BEVESPI AEROSPHERE PI contains information about the use of the drug and potential risks in specific populations. Use the area below to record key takeways regarding the use of BEVESPI AEROSHPERE in each of these specific populations.

Specific Populations	Notes
Pregnancy 	
Labor and delivery 	
Nursing mothers 	

Specific Populations	Notes
Pediatric use 	
Geriatric use 	
Hepatic impairment 	
Renal impairment 	

Overdosage

Learning Objective:

- Discuss options in the event of overdosage with BEVESPI AEROSPHERE

Overdosage of BEVESPI AEROSPHERE

No cases of overdose have been reported with BEVESPI AEROSPHERE. Treatment of overdosage consists of discontinuing BEVESPI AEROSPHERE together with instituting appropriate symptomatic and/or supportive therapy.

Overdosage of Glycopyrrolate

High doses of glycopyrrolate 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 (severe obstruction to the normal flow of feces through the bowels), or difficulties in voiding.

Overdosage of Formoterol Fumarate

An overdose of formoterol fumarate would likely lead to an exaggeration of effects that are typical for beta$_2$ agonists. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol fumarate.

Description

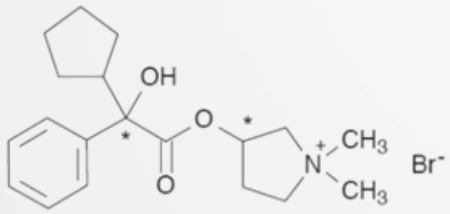
Learning Objectives:

- Identify the active ingredients of BEVESPI AEROSPHERE
- Describe the active ingredients of BEVESPI AEROSPHERE

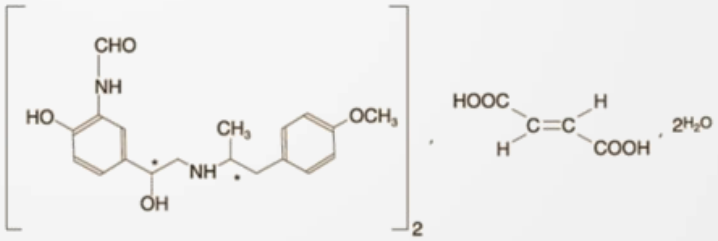
Description

BEVESPI AEROSPHERE Inhalation Aerosol is a pMDI for delivery of a combination of micronized (pulverized to reduce particle size) glycopyrrolate, an anticholinergic, and micronized formoterol fumarate, a LABA, for oral inhalation.

Molecular Structures



Glycopyrrolate



Formoterol fumarate

Clinical Pharmacology

Learning Objectives:

- Describe the mechanism of action of BEVESPI AEROSPHERE
- Describe the pharmacokinetics and pharmacodynamics of BEVESPI AEROSPHERE

Mechanism of Action

BEVESPI AEROSPHERE contains both glycopyrrolate and formoterol fumarate. The mechanisms of action for the individual components apply to BEVESPI AEROSPHERE. These drugs represent 2 different classes of medications (a long-acting muscarinic antagonist and a LABA) that have different effects on clinical and physiologic indices.

- Glycopyrrolate: In the airways, it exhibits pharmacologic effects through inhibition of the M_3 receptor at the smooth muscle, leading to bronchodilation
- Formoterol fumarate: The pharmacologic effects 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

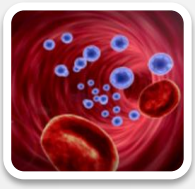
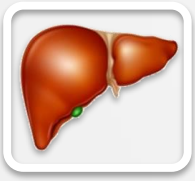
NOTE: For additional details regarding the mechanism of action of BEVESPI AEROSPHERE, please refer to the BEVESPI AEROSPHERE MOA Module.

Pharmacodynamics

The potential for QTc interval prolongation was assessed in healthy subjects. The largest mean differences from placebo in baseline-corrected QTc interval for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. A dose-dependent increase in heart rate was also observed. In patients with COPD, no clinically meaningful effects on cardiac rhythm were observed.

Pharmacokinetics

Linear pharmacokinetics were observed for glycopyrrolate (dose range: 18–144 mcg) and formoterol fumarate (dose range: 2.4–19.2 mcg) after oral inhalation. Use the area below to record any key points you want to remember regarding the pharmacokinetics for BEVESPI AEROSPHERE.

Pharmacokinetic Property	Notes
Absorption 	
Distribution 	
Metabolism 	
Elimination 	

How Supplied/Storage and Handling

Learning Objective:

- Describe how BEVESPI AEROSPHERE is supplied, stored, and handled

How Supplied/Storage and Handling

The key considerations for using BEVESPI AEROSPHERE as outlined in this section of the PI include:

- Each canister contains 120 inhalations
- BEVESPI AEROSPHERE actuator should not be used with any other inhalation drug product
- BEVESPI AEROSPHERE should be discarded when the dose indicator display window shows “0” or 3 months after removal from the foil pouch, whichever comes first
- Never conduct the “float test”, which involves immersing the canister into water to determine the amount remaining in the canister
- Store at controlled room temperature 20°–25°C (68°–77°F); excursions permitted to 15°–30°C (59°–86°F)
- The canister should be at room temperature before use
- Shake well before use
- Keep out of reach of children

Contents under pressure:

- Do not puncture
- Do not use or store near heat or open flame
- Exposure to temperatures above 49°C (120°F) may cause bursting
- Never throw canister into fire or incinerator
- Avoid spraying in eyes

Clinical Studies

Learning Objectives:

- Describe the overall design and methods of the clinical studies cited in the BEVESPI AEROSPHERE PI
- Identify the key efficacy results of the clinical studies cited in the BEVESPI AEROSPHERE PI

Clinical Trial Program

The safety and efficacy of BEVESPI AEROSPHERE were evaluated in a clinical development program that included the following clinical trials:

QUESTION: Which component of the BEVESPI AEROSPHERE clinical development program shown above was NOT included in the efficacy analysis, but WAS used in safety analysis?

Dose-Ranging Trials

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

Confirmatory Trials

2 randomized, double-blind, placebo-controlled, parallel-group, 24-week trials in patients with moderate to very severe COPD

Designed to evaluate the efficacy of BEVESPI AEROSPHERE on lung function

Treatments studied:

- BEVESPI AEROSPHERE (glycopyrrolate 18 mcg/formoterol fumarate 9.6 mcg)
- Glycopyrrolate 18 mcg
- Formoterol fumarate 9.6 mcg
- Placebo

Primary end point:

Change from baseline in trough (predose) forced expiratory volume in 1 second (FEV_1) at week 24 compared with placebo, glycopyrrolate 18 mcg BID, and formoterol fumarate 9.6 mcg BID

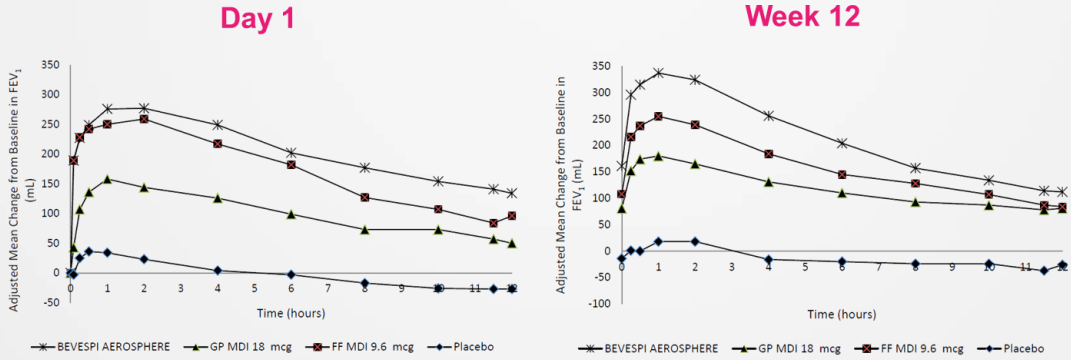
Efficacy Results

Table 2 [BEVESPI AEROSPHERE PI April 2016 Section14.2 Table 2]

Least Squares Mean Change from Baseline in Morning Trough FEV_1 (mL) at Week 24 BEVESPI AEROSPHERE Difference From Placebo, Glycopyrrolate, and Formoterol Fumarate			
	Placebo (95% CI)	**Glycopyrrolate 18 mcg BID (95% CI)**	**Formoterol Fumarate 9.6 mcg BID (95% CI)**
Trial 1	n = 161	n = 344	n = 367
BEVESPI AEROSPHERE N = 429	**150 mL** (114, 186)	**59 mL** (31, 88)	**64 mL** (36, 92)
Trial 2	n = 170	n = 367	n = 350
BEVESPI AEROSPHERE N = 433	**103 mL** (67, 140)	**54 mL** (25, 83)	**56 mL** (27, 85)

QUESTION: What conclusions can be drawn from the table above regarding the efficacy of BEVESPI AEROSPHERE? How are these results described in the PI?

Figure 3: Mean Change From Baseline in Trough FEV_1 Over Time at Day 1 and Week 12 (Trial 1)[1]



[BEVESPI AEROSPHERE PI April 2016 Section14.2 Figure 3]

QUESTION: The 2 graphs above demonstrate the mean change from baseline in trough FEV_1 at day 1 and at week 12. How are these results described in the BEVESPI AEROSPHERE PI?

Efficacy Results (cont.)

St. George's Respiratory Questionnaire (SGRQ) [BEVESPI AEROSPHERE PI April 2016 Section14.2 para7]

	BEVESPI AEROSPHERE	Glycopyrrolate 18 mcg	Formoterol Fumarate 9.6 mcg	Placebo
Trial 1				
SGRQ responder rate[a]	37%	30%	35%	28%
Odds ratio vs BEVESPI AEROSPHERE	N/A	1.4 (95% CI: 1.1, 1.8)	1.1 (95% CI: 0.9, 1.5)	1.5 (95% CI: 1.1, 2.1)
Trial 2				
Odds ratio vs BEVESPI AEROSPHERE	N/A	1.2 (95% CI: 0.9, 1.6)	1.3 (95% CI: 1.0, 1.7)	1.3 (95% CI: 0.9, 1.8)

[a]SGRQ responder rate: Improvement in score of 4 or more as threshold

QUESTION: Describe what the SGRQ is and what type of efficacy data it generates. What value does this data add?

Questions for Reflection

This section of the Companion Guide includes a few Reflective Questions for you to answer upon completion of the respective annotated PI WBT module. Allowing yourself the time to answer these Reflective Questions helps you to better internalize those key concepts and increase retention and transfer of that information to your everyday job.

1. Which do you feel are the most important concepts from the BEVESPI AEROSPHERE annotated PI WBT module?

2. What is the value in what you learned about in the BEVESPI AEROSPHERE annotated PI WBT module?

References

1. BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; April 2016.
2. Taber's Medical Dictionary Online. Unbound Medicine, Inc. Copyright 2000-2014. http://www.tabers.com/tabersonline. Accessed March 11, 2015.