

## PRODUCT MONOGRAPH

Pr **SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup>**

Glycopyrronium inhalation powder hard capsules

50 mcg glycopyrronium as glycopyrronium bromide per capsule

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> capsules to be used only with the supplied  
SEEBRI<sup>®</sup>BREEZHALER<sup>®</sup> inhalation device

Bronchodilator  
(Long-acting muscarinic antagonist)

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SEEBRI is a registered trademark.  
BREEZHALER is a registered trademark.

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Pr **SEEBRI® BREEZHALER®**  
Glycopyrronium inhalation powder hard capsules

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
Oral inhalation	Inhalation powder hard capsules/ contain 50 mcg glycopyrronium as glycopyrronium bromide	Lactose monohydrate, magnesium stearate, hypromellose, purified water, carrageenan, potassium chloride and FDC Yellow 6 (110 Sunset Yellow FCF)

**INDICATIONS AND CLINICAL USE**

SEEBRI® BREEZHALER® (glycopyrronium bromide) is indicated as a long-term once-daily maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

SEEBRI® BREEZHALER® is not indicated for the relief of an acute deterioration of COPD.

**Geriatrics (> 65 years of age):**

SEEBRI® BREEZHALER® can be used at the recommended dose in elderly patients 65 years of age and older.

**Pediatrics (< 18 years of age):**

SEEBRI® BREEZHALER® should not be used in patients under 18 years of age.

**CONTRAINDICATIONS**

SEEBRI® BREEZHALER® (glycopyrronium bromide) is contraindicated in:

- Patients with hypersensitivity to glycopyrronium bromide or to any other component of SEEBRI® BREEZHALER®. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients with severe hypersensitivity to milk proteins.

## WARNINGS AND PRECAUTIONS

### **General**

#### **Not for Acute use**

SEEBRI® BREEZHALER® is a once-daily long-term maintenance treatment and is not indicated for the treatment of acute episodes of bronchospasm, *i.e.* as a rescue therapy.

When beginning treatment with SEEBRI® BREEZHALER®, patients who have been taking inhaled, short-acting bronchodilators on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

When prescribing SEEBRI® BREEZHALER®, the healthcare professional should also provide the patient with an inhaled, short-acting bronchodilator (*i.e.* short-acting beta-agonist) for treatment of COPD symptoms that occur acutely, despite regular once-daily use of SEEBRI® BREEZHALER®.

#### **COPD Deterioration**

SEEBRI® BREEZHALER® should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. The use of SEEBRI® BREEZHALER® in this setting is inappropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If SEEBRI® BREEZHALER® no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta<sub>2</sub>-agonist becomes less effective or the patient needs more inhalation of short-acting beta<sub>2</sub>-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 SEEBRI® BREEZHALER® beyond the recommended dose is not appropriate in this situation.

#### **Excessive Use**

SEEBRI® BREEZHALER® should not be used more frequently than once daily or at higher doses than recommended. SEEBRI® BREEZHALER® should not be administered concomitantly with other medicines containing a long-acting muscarinic antagonist, as this has not been studied, and an overdose may result.

#### **Effects on ability to drive or use machines**

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

#### **Anticholinergic Effects**

Like other anticholinergic drugs, SEEBRI® BREEZHALER® should be used with caution in patients with narrow-angle glaucoma or urinary retention.

### ***Worsening of Narrow-Angle Glaucoma***

SEEBRI® BREEZHALER® should be used with caution in patients with narrow-angle glaucoma. Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of 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. Miotic drops alone are not considered to be effective treatment.

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

SEEBRI® BREEZHALER® should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

## **Cardiovascular**

Cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists. Patients with unstable ischaemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc was prolonged at screening were excluded from the clinical trials. Therefore the experience in these patient groups is limited.

SEEBRI® BREEZHALER® should be used with caution in these patients. In some cases treatment may need to be discontinued.

## **Immune**

### **Hypersensitivity**

Immediate hypersensitivity reactions have been reported after administration of SEEBRI® BREEZHALER®. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips, and face), urticaria, or skin rash, SEEBRI® BREEZHALER® should be discontinued immediately and alternative therapy instituted.

## **Ophthalmologic**

**Worsening of Narrow-Angle Glaucoma (see Anticholinergic Effects).**

## **Renal**

### **Patients with severe renal impairment**

For patients with severe renal impairment (estimated glomerular filtration rate below 30 mL/min/1.73m<sup>2</sup>) including those with end-stage renal disease requiring dialysis, SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> should be used only if the expected benefit outweighs the potential risk (see ACTION AND CLINICAL PHARMACOLOGY). These patients should be monitored closely for potential adverse drug reactions.

**Worsening of Urinary Retention** (see Anticholinergic Effects).

## **Respiratory**

### **Paradoxical bronchospasm**

As with other inhalation therapies, administration of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> should be discontinued immediately and alternative therapy instituted.

## **Special Populations**

**Women of child-bearing potential:** There are no special recommendations for women of child-bearing potential.

**Pregnant Women:** There are no data available on the use of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> in pregnant women. Therefore, SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

**Nursing Women:** It is not known whether glycopyrronium passes into human breast milk. However, glycopyrronium (including its metabolites) was excreted into the milk of lactating rats (See TOXICOLOGY). The use of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

**Pediatrics (< 18 years of age):** SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in patients under 18 years of age.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The safety and tolerability of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> was evaluated at the recommended dose of 50 mcg once-daily in 1353 COPD patients. Of these, 842 patients have been treated for at least 26 weeks (6 months), and 351 patients for at least 52 weeks (12 months). Patients with unstable cardiac disease, long QT syndrome or QT prolongation, narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction were excluded from the studies.

Adverse reactions to SEEBRI® BREEZHALER® are expected to be similar in nature to other muscarinic antagonists and may include cardiovascular effects (atrial arrhythmias and tachycardia), ocular disorders (e.g. blurred vision), urinary retention, gastrointestinal disorders, dry mouth, cough and immediate hypersensitivity reactions. Adverse drug reactions to SEEBRI® BREEZHALER® related to local tolerability included throat irritation, nasopharyngitis, rhinitis and sinusitis.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse drug reactions with SEEBRI® BREEZHALER® reported during the first 6 months of two pooled pivotal Phase III trials of 6- and 12-months duration are listed by MedDRA system organ class (Table 1). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.

**Table 1 - Adverse drug reactions ≥1.0% in pooled COPD safety database**

<b>COPD 6-month safety database</b>		
<b>Adverse drug reactions</b>	<b>Glycopyrronium bromide 50mcg once daily n=1075<sup>1</sup> N (%)<sup>2</sup></b>	<b>Placebo n=535<sup>1</sup> N (%)<sup>2</sup></b>
<b>Gastrointestinal disorders</b>		
- Dry mouth	26 (2.4)	6 (1.1)
- Gastroenteritis	15 (1.4)	5 (0.9)
<b>Psychiatric disorders</b>		
- Insomnia	11 (1.0)	4 (0.8)
<b>COPD 12-month safety database</b>		
	<b>n=525 N (%)</b>	<b>n=268 N (%)</b>
<b>Infections and infestations</b>		
- Nasopharyngitis	47 (9.0)	15 (5.6)
- Rhinitis	9 (1.7)	2 (0.7)
<b>Gastrointestinal disorders</b>		
- Dry mouth	16 (3.0)	5 (1.9)
- Gastroenteritis	14 (2.7)	1 (0.4)
- Dyspepsia	7 (1.3)	1 (0.4)

- Vomiting	7 (1.3)	2 (0.7)
<b>Musculoskeletal and connective tissue disorders</b>		
- Musculoskeletal pain	13 (2.4)	2 (0.7)
- Neck pain	7 (1.3)	2 (0.7)
- Pain in extremity	6 (1.1)	2 (0.7)
<b>Cardiac disorders</b>		
- Atrial fibrillation	7 (1.3)	2 (0.7)
<b>Renal and urinary tract disorders</b>		
- Dysuria	6 (1.1)	0
<b>Metabolism and nutrition disorders</b>		
- Hyperglycemia	6 (1.1)	2 (0.7)
<b>Respiratory, thoracic and mediastinal disorders</b>		
- Sinus congestion	6 (1.1)	2 (0.7)

<sup>1</sup>n= number of patients analysed

<sup>2</sup>N= number of patients with an adverse reaction

The most common anticholinergic adverse drug reaction was dry mouth. The majority of the reports of dry mouth were suspected to be drug related and of mild degree, none was severe. Rash was uncommon and generally mild.

### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

**Cardiac disorders:** palpitations

**Gastrointestinal disorders:** dental caries

**General disorders and administration site conditions:** fatigue, asthenia

**Infections and infestations:** cystitis

**Metabolism and nutrition disorders:** diabetes mellitus

**Nervous system disorders:** hypoesthesia

**Renal and urinary disorders:** urinary retention

**Respiratory, thoracic and mediastinal disorders:** productive cough, throat irritation, epistaxis

**Skin and subcutaneous tissue disorders:** rash

### **Special populations**

In elderly patients above 75 years of age the frequencies of urinary tract infection and headache were higher on SEEBRI® BREEZHALER® than on placebo, with 3.0 versus 1.5% and 2.3 versus 0%, respectively.

## **Post-Market Adverse Drug Reactions**

The following adverse drug reactions have been reported with SEEBRI® BREEZHALER® in post-marketing experience. 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.

**Immune system disorders:** hypersensitivity, angioedema.

**Respiratory, thoracic and mediastinal disorders:** paradoxical bronchospasm, dysphonia

**Skin and subcutaneous tissue disorders:** pruritus

## **DRUG INTERACTIONS**

Although no formal drug interaction studies have been performed, in clinical studies SEEBRI® BREEZHALER® has been used concomitantly with other drugs commonly used to treat COPD including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids. No safety findings were observed to contraindicate administration of these agents with SEEBRI® BREEZHALER®.

### **Drug-Drug Interactions**

#### **Anticholinergics**

There is a potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid co-administration of SEEBRI® BREEZHALER® with other anticholinergic-containing drugs as this may lead to an increase in undesirable anticholinergic effects.

#### **Cimetidine and other inhibitors of organic cation transport**

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when SEEBRI® BREEZHALER® is co-administered with cimetidine or other inhibitors of the organic cation transporter.

*In vitro*, glycopyrronium was a substrate for the multidrug and toxin extrusion protein MATE1 found on renal tubule cells. Therefore the plasma levels of glycopyrronium may be increased by inhibitors of MATE1, and the plasma levels of MATE1 substrates may be increased by glycopyrronium. No clinical drug interaction studies were performed. Other *in vitro* studies showed that SEEBRI® BREEZHALER® is not likely to inhibit or induce the metabolism of other drugs. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see CLINICAL PHARMACOLOGY). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

**Table 2 - Established or Potential Drug-Drug Interactions**

<b>Proper Name</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comment</b>
<i>cimetidine</i>	CT	Increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%.	Based on the magnitude of these changes, no clinically relevant drug interaction is expected when SEEBRI® BREEZHALER® is co-administered with cimetidine or other inhibitors of the organic cation transport in patients with normal renal function.

Legend: C = Case Study; CT = Clinical Trial; CS = Class Statements; T = Theoretical

## **DOSAGE AND ADMINISTRATION**

### **Dosing considerations**

- Counseling by doctors on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.
- Elderly patients, hepatically impaired patients, and renally impaired patients can use SEEBRI® BREEZHALER® at the recommended dose. However, as with all renally excreted drugs, SEEBRI® BREEZHALER® use should be monitored closely in patients with renal impairment or end stage renal disease.
- There is no experience with SEEBRI® BREEZHALER® in infants and children and therefore it should not be used in this age group.

### **Recommended Dose**

The recommended dosage of SEEBRI® BREEZHALER® is the once-daily oral inhalation of the content of one 50 mcg capsule using the SEEBRI® BREEZHALER® inhaler. The clinical trials were conducted based on dosing in the morning.

**The capsule must not be swallowed.**

### **Dosing in special populations**

#### **Renal impairment**

SEEBRI® BREEZHALER® can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis SEEBRI® BREEZHALER® should be used only if the expected benefit outweighs the potential risk (See also WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

## **Hepatic impairment**

No specific studies have been conducted in patients with hepatic impairment. SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> is predominantly cleared by renal excretion and therefore no major increase in exposure is expected in patients with hepatic impairment. No dose adjustment is required in patients with hepatic impairment.

## **Geriatric patients**

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> can be used at the recommended dose in elderly patients 65 years of age and older.

## **Pediatric patients**

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> should not be used in patients under 18 years of age.

## **Administration**

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> is recommended for once-daily administration at the same time each day.

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> capsules must be administered only by the oral inhalation route and only using the SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> inhaler. SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> capsules must not be swallowed (see also OVERDOSAGE).

SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> capsules must always be stored in the blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE.

When prescribing SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup>, patients should be instructed on the correct use of the inhaler. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

## **Missed Dose**

If a dose is missed, the next dose should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

## **OVERDOSAGE**

High doses of glycopyrronium may lead to signs and symptoms of exaggerated anticholinergic effects for which symptomatic treatment may be indicated. Such effects may include increased intraocular pressure causing pain, vision disturbances or reddening of the eye, obstipation or voiding difficulties.

In COPD patients, repeated orally inhaled administration of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> at total doses of 100 and 200 mcg once-daily for 28 days were well tolerated.

Acute intoxication by inadvertent oral ingestion of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> capsules is unlikely due to the low oral bioavailability (about 5%).

Peak plasma levels and total systemic exposure following a single i.v. administration of 120 mcg glycopyrronium in healthy volunteers were about 50-fold and 6-fold higher, respectively, than the peak and total systemic exposure at steady-state achieved with the recommended dose (50 mcg inhaled once-daily) of SEEBRI® BREEZHALER® in COPD patients and were well tolerated.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

SEEBRI® BREEZHALER® is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic) for once-daily maintenance bronchodilator treatment of COPD. Parasympathetic nerves are the major bronchoconstrictive neural pathway in airways, and cholinergic tone is the key reversible component of airflow obstruction in COPD. SEEBRI® BREEZHALER® works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells thereby dilating the airways.

Of the five known muscarinic receptor subtypes (M1-5), only subtypes M1-3 have a defined physiological function in the human lung. Glycopyrronium is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M3 and M1 receptors over the human M2 receptor in competition binding studies. It has a rapid onset of action as evidenced by observed receptor association/dissociation kinetic parameters and the onset of action after inhalation in clinical studies.

The long duration of action can be partly attributed to sustained drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the SEEBRI® BREEZHALER® inhaler in contrast to the half-life after i.v. administration (see ACTION AND CLINICAL PHARMACOLOGY). Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide provides further evidence for this.

### **Pharmacodynamics**

#### **Primary Pharmacodynamic Effects**

SEEBRI® BREEZHALER® increased trough FEV<sub>1</sub> (mean of 23 h. 15 min. and 23 h. 45 min. post dose) compared to placebo at Week 12 in the 6 month and 12 month pivotal studies by 0.108L and 0.097L respectively. This effect was maintained throughout the study duration. Serial spirometry was performed over 24h post dosing in both studies and showed that SEEBRI® BREEZHALER® significantly increased FEV<sub>1</sub> over 24 hours compared to placebo.

In the pivotal studies there was a rapid onset of action within 5 minutes after inhalation of SEEBRI® BREEZHALER®, with an increase in FEV<sub>1</sub> relative to baseline ranging from 0.091 L to 0.094 L.

## Secondary Pharmacodynamic Effects

The effect on heart rate and QTc interval of 120 mcg glycopyrronium administered intravenously was investigated in young healthy subjects. Peak exposures (C<sub>max</sub>) about 50-fold higher than after inhalation of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> 50 mcg at steady state were achieved and did not result in tachycardia or QT(c) prolongation. Mild bradycardia was observed (mean difference over 24 hours was a reduction by 2 bpm when compared to placebo), which is a known effect of low exposures to anticholinergic compounds in young healthy subjects. In a thorough QT study in 73 healthy volunteers, a single inhaled dose of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> 352 micrograms (8 times the therapeutic dose) did not prolong the QTc interval and slightly reduced heart rate (maximal effect 5.9 bpm; average effect over 24 hours 2.8 bpm) when compared to placebo. No changes in heart rate or QT(c) interval were observed with SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> 200 mcg in COPD patients.

## Pharmacokinetics

**Table 3 - Summary of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup>'s Pharmacokinetic Parameters in COPD patients**

Mean (Standard Deviation)	C <sub>max</sub> [pg/mL]	T <sub>½</sub> (h)	AUC <sub>0-24h</sub> [pg*h/mL]	Renal Clearance (CL <sub>r</sub> ) [L/h]	Volume of distribution (V <sub>ss</sub> ) <sup>3)</sup> [L]
Single dose	146 (109)	52.5 (12.7) <sup>1)</sup>	n.d.	23.1 (7.46) <sup>1)</sup>	82.7 (21.7) <sup>1)</sup>
Multiple dose (steady state)	166 (97.3)	13.4 (8.02) <sup>2)</sup> 20.8 (8.61) <sup>2)</sup> 21.6 (3.24) <sup>2)</sup>	464 (213)	17.6 (6.4)	n.d.

Notes: n.d.= not determined; <sup>1)</sup> Determined in a biopharmaceutical study in healthy volunteers; <sup>2)</sup> Determined in a pharmacokinetic study in COPD patients for doses of 50, 100 and 200 mcg respectively <sup>3)</sup> Steady-state volume of distribution (V<sub>ss</sub>), determined in a biopharmaceutical study in healthy volunteers

## Absorption

Following oral inhalation using the SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> inhaler, glycopyrronium was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of glycopyrronium inhaled via SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> inhaler was estimated to be about 40%. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption. The absolute bioavailability of orally administered glycopyrronium (400 mcg) was estimated to be about 5%.

Following repeated once-daily inhalation in patients with COPD, the pharmacokinetic (PK) steady-state of glycopyrronium was reached within one week of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium for a 50 mcg once-daily dosing regimen were 166 pg/mL and 8 pg/mL, respectively. With once-daily doses of 100 and 200 mcg, steady-state exposure to glycopyrronium (AUC over the dosing interval) was about 1.4-to 1.7-fold higher than after the first dose. Urinary excretion data at steady-state compared to the first dose suggest that systemic accumulation is independent of dose in the dose range of 25 to 200 mcg.

## Distribution

After i.v. dosing, the steady-state volume of distribution ( $V_{ss}$ ) of glycopyrronium was 83 L and the volume of distribution in the terminal phase ( $V_z$ ) was 376 L. The apparent volume of distribution in the terminal phase following inhalation ( $V_z/F$ ) was 7310 L, which reflects the much slower elimination after inhalation. The *in vitro* human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL. These concentrations were at least 6-fold higher than the steady state mean peak level achieved in plasma for a 50 mcg once-daily dosing regimen.

## Biotransformation/metabolism

*In vitro* metabolism studies showed consistent metabolic pathways for glycopyrronium between animals and humans. No human specific metabolites were found. Hydroxylation resulting in a variety of mono- and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen.

*In vitro* investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. The hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family.

After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since *in vitro* studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug  $C_{max}$  and AUC) after i.v. administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium by pre-systemic hydrolysis and/or via first pass metabolism. After inhalation as well as i.v. administration, only minimal amounts of M9 were found in the urine (i.e.  $\leq 0.5\%$  of dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

*In vitro* inhibition studies demonstrated that glycopyrronium has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR. *In vitro* enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

## Elimination

After i.v. administration of [ $^3H$ ]-labelled glycopyrronium bromide to humans, the mean urinary excretion of radioactivity in 48 h amounted to 85% of the dose. A further 5% of the dose was found in the bile. Thus, mass balance was almost complete.

Renal elimination of parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium whereas non-renal clearance processes account for about 30 to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 50 and 200 mcg glycopyrronium by healthy volunteers and patients with COPD mean renal clearance of

glycopyrronium was in the range of 17.4 and 24.4 L/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20% of the dose was found in urine as parent drug.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life in healthy volunteers was much longer after inhalation (33 to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 hours after inhalation.

### **Special Populations and Conditions**

A population PK analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. COPD patients with lower body weights (40 – 50 kg) had higher systemic exposure (41%) compared to those with higher body weights (90 – 100 kg). However, SEEBRI® BREEZHALER® 50 mcg once-daily can be safely used in all body weight groups. Dose adjustment is not necessary for patients aged 65 years and older.

Gender, smoking status and baseline FEV<sub>1</sub> had no apparent effect on systemic exposure.

### **Ethnicity**

An ethnic sensitivity study conducted in Japanese and Caucasian healthy volunteers showed peak plasma exposure was on average 80% higher and total systemic exposure (AUC) and urinary excretion were 38 to 46% higher in Japanese than in Caucasian volunteers. The renal clearance (CL<sub>r</sub>) was similar for both populations. The apparent difference in total exposure may reflect differences in systemic uptake of glycopyrronium via the lungs between the two populations. SEEBRI® BREEZHALER® 50 mcg once-daily can be safely used in the two populations. Insufficient PK data is available for other ethnicities or races.

### **Patients with hepatic impairment**

Clinical studies in patients with hepatic impairment have not been conducted. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion (see Pharmacokinetics). Impairment of the hepatic metabolism of glycopyrronium is not expected to result in a clinically relevant increase of systemic exposure.

### **Patients with renal impairment**

Renal impairment has an impact on the systemic exposure to glycopyrronium. A moderate mean increase in total systemic exposure (AUC<sub>last</sub>) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease. In COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate eGFR<sub>≥</sub>30 mL/min/1.73m<sup>2</sup>), SEEBRI® BREEZHALER® can be used at the recommended dose. There is no long term experience in patients with renal impairment.

## STORAGE AND STABILITY

Store SEEBRI® BREEZHALER® at room temperature between 15-25°C. Do not store above 25°C and protect from moisture.

Keep out of the reach of children.

## SPECIAL HANDLING INSTRUCTIONS

- SEEBRI® BREEZHALER® capsules should be used with the SEEBRI® BREEZHALER® inhalation device only. The SEEBRI® BREEZHALER® inhalation device should not be used with any other capsules.
- Capsules should always be stored in the blister and only removed from the blister immediately before use.
- Always use the new SEEBRI® BREEZHALER® inhalation device provided with each new prescription and discard the old device.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

SEEBRI® BREEZHALER® is available as 50 mcg, inhalation powder hard capsules.

**50 mcg SEEBRI® BREEZHALER® contains:** Aluminium blister-packaged glycopyrronium as (glycopyrronium bromide) transparent orange capsules with the product code GPL50 printed in black above a black bar and the Novartis company logo printed under a black bar.

Each capsule contains 63 mcg glycopyrronium bromide equivalent to 50 mcg glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the SEEBRI® BREEZHALER® inhaler) is equivalent to 44 mcg glycopyrronium.

Each capsule also contains lactose monohydrate and magnesium stearate.

The capsule shell components are hypromellose, purified water, carrageenan, potassium chloride and FDC Yellow 6 (110 Sunset Yellow FCF).

The following pack types are available:

- Carton of 30 SEEBRI® BREEZHALER® capsules (3 blister cards) and one SEEBRI® BREEZHALER® device.
- Carton of 10 SEEBRI® BREEZHALER® capsules (1 blister card) and 5 SEEBRI® BREEZHALER® devices.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

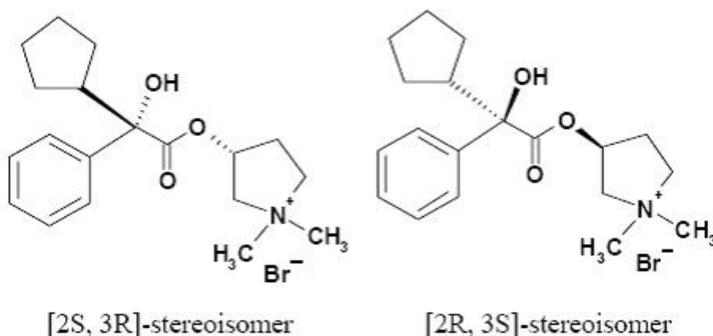
#### Drug Substance

Proper name: Glycopyrronium bromide

Chemical name: 3-(2-Cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidinium bromide

Molecular formula and molecular mass:  $C_{19}H_{28}NO_3$  Br  
Salt form on anhydrous basis: 398.33

Structural formula:



Physicochemical properties:

The drug substance glycopyrronium bromide presents 2 asymmetric carbon atoms and is an optically inactive racemic mixture of 2 stereoisomers (2S, 3R and 2R, 3S), hereafter referred to as the stereoisomers (S,R) and (R,S).

The pH of glycopyrronium bromide in 1.0% m/V (g/100 mL) solution in water at room temperature is 6.0.

Melting range: 193 – 198 °C (but the range between beginning and end of melting does not exceed 2 °C).

#### SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> INHALATION DEVICE

The SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> is a plastic inhalation device used for inhaling the content of SEEBRI<sup>®</sup> BREEZHALER<sup>®</sup> (glycopyrronium bromide) capsules. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time.

## CLINICAL TRIALS

The SEEBRI® BREEZHALER® Phase III clinical development program consisted of two key studies (a 6-month placebo-controlled study and a 12-month placebo and active-controlled study). These studies enrolled 1888 patients with a clinical diagnosis of COPD, who were 40 years old or older, had a smoking history of at least 10 pack years, had a post-bronchodilator FEV<sub>1</sub> <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV<sub>1</sub>/FVC ratio of less than 70%.

### Study demographics and trial design

**Table 4 - Summary of patient demographics for clinical trials in specific indication**

Study #	Trial design Dosage, route of administration and duration	Study subjects‡ (n=number)	Mean age (Range)	Gender
A2303	52-week treatment, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of Glycopyrronium (50 mcg o.d.) in patients with COPD, using open label tiotropium (18 mcg o.d) as an active control	Total: n = 1060 Glycopyrronium 50 mcg o.d.: n = 525 Placebo: n = 268 Open Label Tiotropium 18 mcg o.d.: n = 267	63.6 years (41- 87)	Male: 680 Female: 380
A2304	26-week treatment, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety and tolerability of Glycopyrronium (50 mcg o.d.) in patients with COPD	Total: n = 817 Glycopyrronium 50 mcg o.d.: n = 550 Placebo: n = 267	63.9 years (40- 91)	Male: 669 Female: 148

‡ Number of patients exposed to treatment or placebo

### Overview of Results

Assessment of efficacy in trials A2304 and A2303 was based on FEV<sub>1</sub>. The primary efficacy endpoint was 24-hour post-dose trough FEV<sub>1</sub> (defined as the average of two FEV<sub>1</sub> measurements taken after 23 hours 10 minutes and 23 hours 45 minutes after the previous dose) after 12 weeks of treatment. Other efficacy variables included: Transition dyspnoea index (TDI), Health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ), time to first moderate or severe COPD exacerbation, rescue medication usage, COPD symptoms (recorded using an electronic patient diary) and FEV<sub>1</sub>, FVC and IC assessed at various time points over the treatment period.

## Lung function

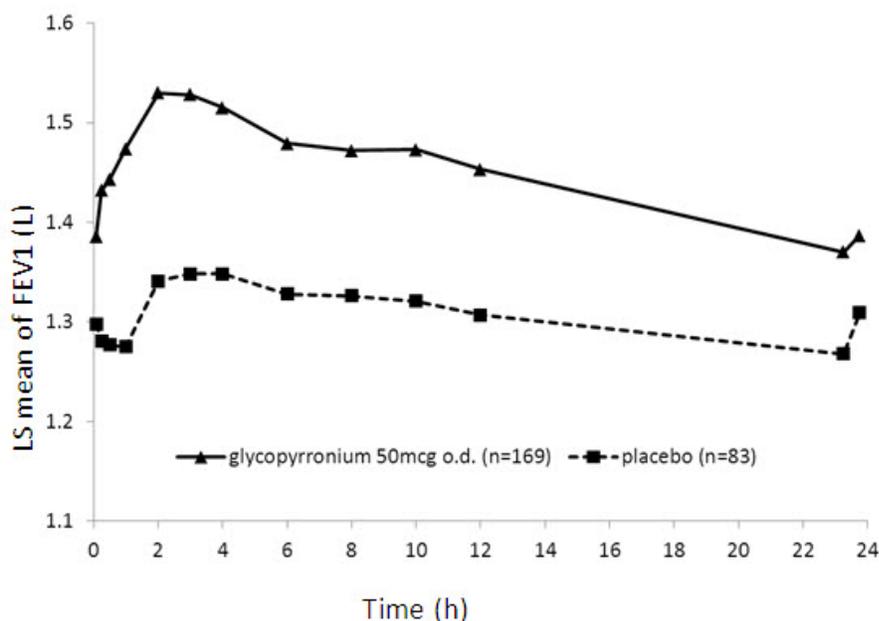
Inhalation of SEEBRI® BREEZHALER® at 50 mcg once-daily resulted in statistically significantly greater bronchodilation as measured by 24-hour post-dose trough FEV<sub>1</sub> at 12 weeks (primary efficacy end-point) compared to placebo. The treatment difference compared to placebo was 0.108 L and 0.097 L (p<0.001) for the 6- and 12-month study respectively. Mean trough FEV<sub>1</sub> for SEEBRI® BREEZHALER® was increased by 0.113 L at week 26 in the 6-month study and 0.108 L at week 52 in the 12-month study, compared to placebo.

In both studies SEEBRI® BREEZHALER® demonstrated a rapid onset of bronchodilator effect within 5 minutes after inhalation. In the 6-month study the increase in FEV<sub>1</sub> was 0.093 L compared to placebo at 5 minutes, increasing to 0.144 L at 15 minutes after the first dose (both p<0.001). In the 12-month study the increase in FEV<sub>1</sub> was 0.087 L at 5 minutes and 0.143 L at 15 minutes after the first dose compared to placebo (p<0.001).

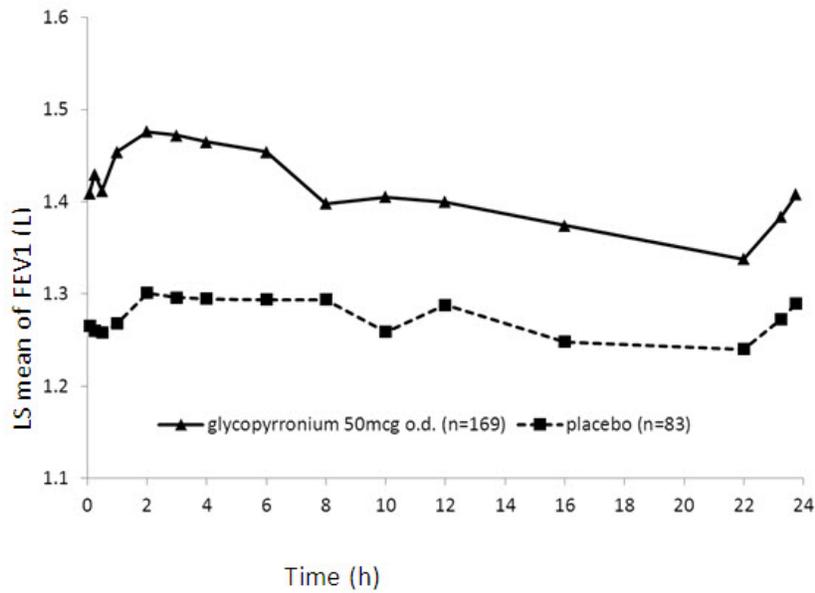
In the 6-month study serial spirometry was performed on Day 1 (Figure 1), Week 12 (Figure 2) and Week 26. In the 12 month study serial spirometry was performed on Day 1 (Figure 3), Week 12 (Figure 4) and Week 52 (Figure 5).

Serial spirometry data was used to calculate FEV<sub>1</sub> standardized (for time) area under the curve (AUC). In the 6-month study, FEV<sub>1</sub> AUC<sub>0-24h</sub> for SEEBRI® BREEZHALER® was 0.133 L and 0.199 L compared to placebo at Week 12 and Week 26 respectively (p<0.001). In the 12-month study FEV<sub>1</sub> AUC<sub>0-24h</sub> for SEEBRI® BREEZHALER® was 0.106 L (p<0.001) compared to placebo both at 12 and at 52 weeks.

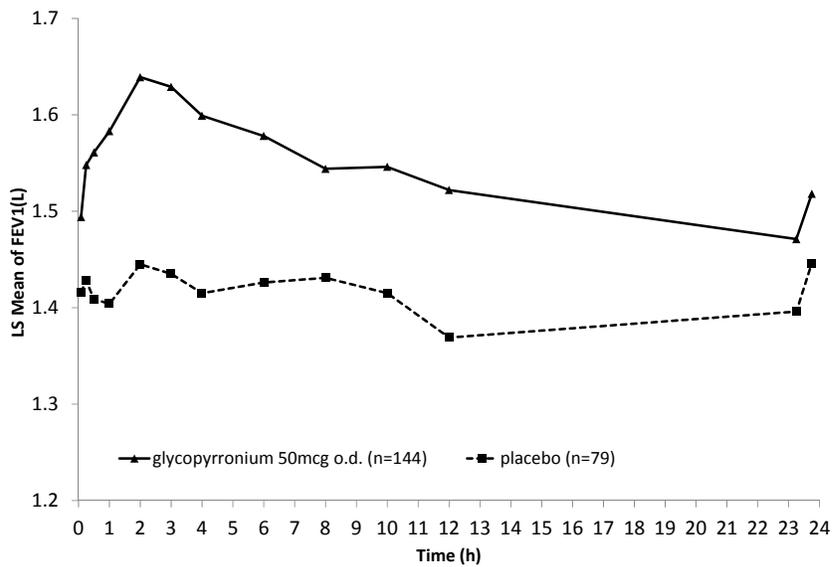
**Figure 1 - Six-month pivotal study: Serial spirometry data (least square means of FEV<sub>1</sub> (L)) after first dose**



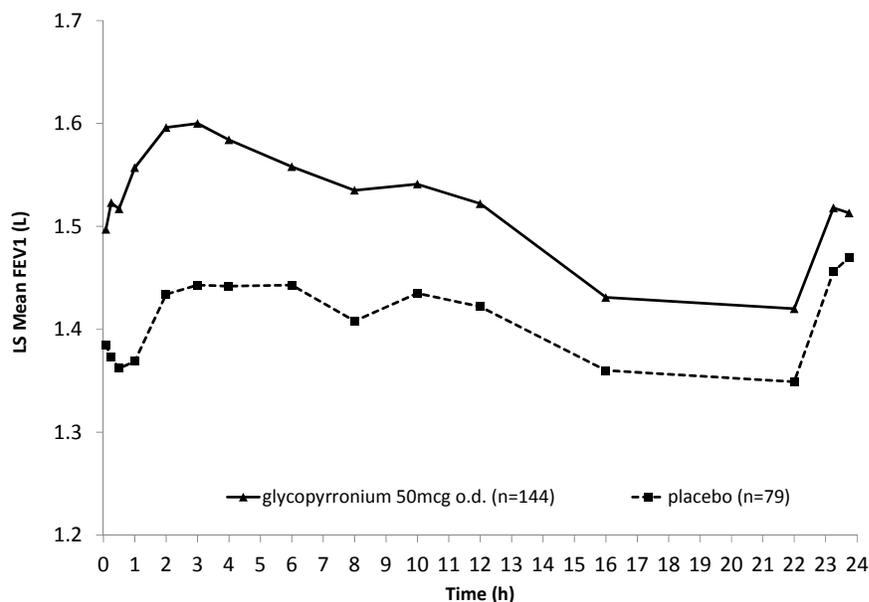
**Figure 2 - Six-month pivotal study: Serial spirometry data (least square means of FEV<sub>1</sub> (L)) at week 12**



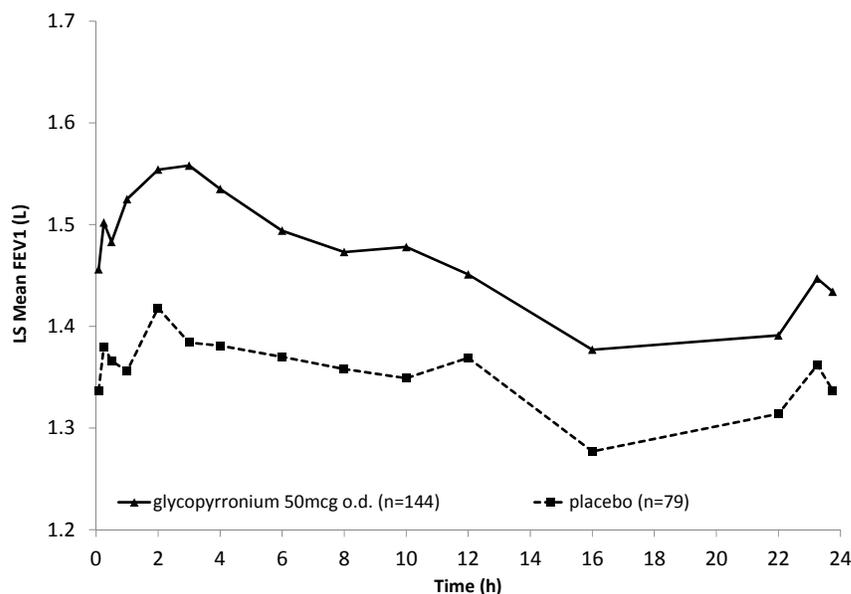
**Figure 3 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV<sub>1</sub> (L)) after first dose**



**Figure 4 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV<sub>1</sub> (L)) at week 12**



**Figure 5 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV<sub>1</sub> (L)) at week 52**



SEEBRI® BREEZHALER® increased mean trough FVC at Week 12 by 0.194 L and 0.183 L compared to placebo ( $p < 0.001$ ) in the 6- and 12-month studies respectively. SEEBRI® BREEZHALER® increased trough inspiratory capacity at Week 12 by 0.097 L and 0.129 L ( $p \leq 0.001$ ) compared to placebo in the 6- and 12-month studies, respectively.

## Symptom Related Outcomes

SEEBRI® BREEZHALER® was shown to reduce dyspnea assessed by the Transition Dyspnea Index (TDI) focal score, improve health status assessed by the St. George's Respiratory Questionnaire (SGRQ) total score, reduce rescue medication usage, and prolong time to first moderate or severe COPD exacerbation (moderate exacerbations were those requiring treatment with systemic corticosteroids and/ or antibiotics, severe exacerbations were those resulting in hospitalization) in the 6 month (Table 5) and 12 month (Table 6) phase III pivotal studies.

**Table 5 – 6 Month pivotal study data**

**Analysis of Covariance (ANCOVA) of dyspnea, health status and rescue medication usage endpoints in 6 month pivotal study**

Endpoint	Treatment	n	Baseline	Treatment	SEEBRI® BREEZHALER® 50 mcg o.d. v.s. placebo -Treatment difference-		
			Mean	LS Mean (SE)	LS Mean (SE)	95% CI	p-value
TDI focal score at Week 26	SEEBRI® BREEZHALER® 50 mcg o.d. (N=534)	493	6.18	1.84 (0.257)	1.04 (0.235)	(0.583, 1.504)	<0.001
	Pbo (N=260)	240	6.30	0.80 (0.294)			
SGRQ total score at Week 26	SEEBRI® BREEZHALER® 50 mcg o.d. (N=534)	502	46.11	39.50 (0.813)	-2.81 (0.961)	(-4.700, -0.926)	0.004
	Pbo (N=260)	246	46.34	42.31 (0.992)			
Change from baseline in mean daily number of puffs of rescue medication over 26 Weeks	SEEBRI® BREEZHALER® 50 mcg o.d. (N=534)	529	4.04	-1.21 (0.122)	-0.46 (0.164)	(-0.784, -0.141)	0.005
	Pbo (N=260)	259	4.05	-0.75 (0.156)			

**Cox-regression analysis of time to first moderate or severe COPD exacerbation in 6 month pivotal study**

Endpoint	Treatment	n / N' (%)	SEEBRI® BREEZHALER® 50 mcg o.d. v.s. place		
			Hazard Ratio	95% CI	p-value
Time to first moderate or severe COPD exacerbation	SEEBRI® BREEZHALER® 50 mcg o.d. (N=534)	93 / 532 (17.5)	0.69	(0.500, 0.949)	0.023
	Pbo (N=260)	63 / 260 (24.2)			

n = patients with a moderate or severe COPD exacerbation, N' = number of patients included in the analysis.

**Table 6 – 12 Month pivotal study data**

**Analysis of Covariance (ANCOVA) of dyspnea, health status and rescue medication usage endpoints in 12 month pivotal study**

Endpoint	Treatment	n	Baseline Treatment		SEEBRI® BREEZHALER® 50 mcg o.d. v.s. placebo -Treatment difference-		
			Mean	LS Mean (SE)	LS Mean (SE)	95% CI	p-value
Transition Dyspnea Index (TDI) at Week 26	SEEBRI® BREEZHALER® 50 mcg o.d. (N=525)	470	6.06	2.13 (0.240)	0.81 (0.260)	(0.299, 1.320)	0.002
	Pbo (N=268)	217	5.95	1.32 (0.289)			
St. George's Respiratory Questionnaire (SGRQ) at Week 52	SEEBRI® BREEZHALER® 50 mcg o.d. (N=525)	499	50.33	40.85 (0.854)	-3.32 (1.004)	(-5.287, -1.346)	<0.001
	Pbo (N=268)	248	50.44	44.16 (1.040)			
Change from baseline in mean daily number of puffs of rescue medication over 52 Weeks	SEEBRI® BREEZHALER® 50 mcg o.d. (N=525)	523	5.21	-1.58 (0.151)	-0.37 (0.181)	(-0.729, -0.019)	0.039
	Pbo (N=268)	263	4.83	-1.20 (0.184)			

**Cox-regression analysis of time to first moderate or severe COPD exacerbation in 12 month pivotal study**

Endpoint	Treatment	n / N' (%)	SEEBRI® BREEZHALER® 50 mcg o.d. v.s. placebo		
			Hazard Ratio	95% CI	p-value
Time to first moderate or severe COPD exacerbation	SEEBRI® BREEZHALER® 50mcg o.d. (N=525)	172 / 524 (32.8)	0.66	(0.520, 0.850)	0.001
	Pbo (N=268)	107 / 266 (40.2)			

n = patients with a moderate or severe COPD exacerbation, N' = number of patients included in the analysis.

### Exercise tolerance and dynamic hyperinflation

In a three week cross-over study evaluating exercise tolerance during a constant work rate cycle ergometer challenge, SEEBRI® BREEZHALER® increased exercise endurance time by 89 seconds,  $p < 0.001$  (an increase of 21 %) compared to placebo. Inspiratory capacity under exercise, a measure of dynamic hyperinflation, was increased by 0.200 L ( $p < 0.001$ ) at isotime compared to placebo.

## DETAILED PHARMACOLOGY

### Clinical Pharmacology

#### Pharmacodynamics

*In vitro* studies have shown that glycopyrronium bromide is a competitive, high affinity muscarinic receptor antagonist. It demonstrated 4- to 5-fold selectivity for the human M3 (pKi value: 9.59) and M1 receptors over the human M2 receptor in competition binding studies. It has a rapid onset of action as evidenced by observed receptor association/dissociation kinetic parameters and the onset of action after inhalation in clinical studies.

The contractile response of isolated rat trachea in response to a muscarinic agonist was studied following treatment with glycopyrronium bromide. Glycopyrronium bromide inhibited contraction with a rapid onset of action ( $\leq 15$  minutes). Using an *in vivo* Rhesus model of muscarinic agonist-induced bronchoconstriction direct delivery of glycopyrronium bromide to the lung induced dose and time-dependent inhibition of methacholine-induced bronchoconstriction with a rapid onset of action ( $\leq 15$  minutes). The duration of action of glycopyrronium bromide was investigated using an *in vivo* model of bronchoconstriction in Brown Norway rats. Muscarinic agonist-induced bronchoconstriction was markedly reduced by intratracheal instillation of glycopyrronium bromide and this effect was maintained 24h post-dose.

## TOXICOLOGY

### Acute Toxicity

Extensive data are reported in the literature for glycopyrronium bromide following single oral, intra-peritoneal or intravenous administrations to mice, rats, rabbits, dogs and cats ([Franko et al 1962](#)), ([Franko et al 1970](#)), ([Saito et al 1973](#)). Further single dose investigations were also included in dose-range finding studies during an intravenous cardiovascular safety pharmacology study in dogs and a 1-week inhalation toxicity study in dogs. These studies revealed clinical signs that included mydriasis, dry nose, dry mucous mouth membranes, tachycardia, prostration, anorexia, hypertrophy of the salivary glands, and diarrhea consistent with exaggerated pharmacological effects and, at very high doses, necrotizing inflammation of the larynx and drug-induced deaths.

### Repeat-dose Toxicity

The effects seen during repeated-dose inhalation toxicity studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium or mild local irritation. These included mild to moderate increases in heart rates in dogs and a number of reversible changes in rat and dogs associated with reduced secretions from the salivary, lacrimal and Harderian glands and pharynx. Lens opacities observed during chronic studies in rats have been described for other muscarinic antagonists and are considered to be species-specific changes. Findings in the respiratory tract of rats included degenerative/regenerative changes and inflammation in the nasal cavity and larynx that are consistent with mild local irritation. Minimal epithelial changes in the lung at the bronchioloalveolar junction were also observed in rats and

are regarded as a mild adaptive response. All these findings were observed at exposures considered to be sufficiently in excess of the maximum human exposure.

**Table 7 - Repeat-dose Toxicity**

Study Type	Species	Route	Doses (mg/kg/day)	Primary findings
7 days	Mouse/ CD-1	Oral gavage	0, 30, 100, 300	Mortality occurred at 300 mg/kg/day. Clinical signs observed at 300 mg/kg/day, consisted of piloerection, diarrhea, hunched posture, and of non-weight bearing of a hindlimb. Morphological changes were seen in the salivary glands, lungs, liver, large intestine, and thymus at $\geq 100$ mg/kg/day, as well as in spleen and mesenteric lymph nodes at 300 mg/kg/day. NOAEL = 30 mg/kg/day
4-weeks	Mouse/ CB6F1	Oral gavage	0, 225 (males only), 300, 500 (females only), 750	Dose levels of 750 mg/kg in males and females for one day, 500 mg/kg/day in females for 5 days, 300 mg/kg/day in males and females and 225 mg/kg/day in males for 28 days resulted in moribundity and mortality. Histopathology findings in the adrenal gland, heart, liver, mandibular lymph node, mandibular salivary gland, mesenteric lymph node, parotid salivary gland, spleen, and thymus were consistent with poor general condition. NOAEL not determined
4-week with 2-week recovery	Wistar Rat	Inhalation	0, 0.08, 0.49, 3.39	Persistent mydriasis, reduced body weight gain and food intake and increased water intake.  Histopathology changes in the salivary glands (increased weight, acinar atrophy or hypertrophy), Harderian glands (porphyrin deposition and acinar hypertrophy), lacrimal glands (diffuse acinar atrophy), nasal cavities (hyaline inclusions in the olfactory respiratory epithelium) and larynx (squamous metaplasia). NOAEL = 0.49 mg/kg/day
13-week	Wistar Rat	Inhalation	0, 0.09, 0.58, 3.56	Reduced body weight gain and food intake; increased neutrophil counts; effects on pupillary diameter.  Histopathology changes in the Harderian glands (porphyrin deposition and acinar cell basophilia), nasal cavities (eosinophilic globules in the respiratory/olfactory epithelium, hypertrophy/hyperplasia of goblet cells and occasional exudate, inflammation and squamous metaplasia of the respiratory epithelium), larynx (squamous metaplasia) and lung (minimal bronchioloalveolar epithelial hypertrophy). NOAEL = 0.58 mg/kg/day.
26-week with 4-week recovery	Wistar Rat	Inhalation	0, 0.07, 0.54, 3.98	Reduced body weight gain and food intake; increased neutrophil counts; effects on pupillary diameter and lenticular changes (slight anterior capsular opacities, anterior prominent suture lines and anterior punctuate cataracts).  Histopathology changes in the Harderian glands (porphyrin deposition), nasal cavities (eosinophilic globules in the respiratory/olfactory epithelium, hypertrophy/hyperplasia of goblet cells and occasional exudate, inflammation, squamous metaplasia of the respiratory epithelium and degeneration of the olfactory epithelium), larynx (squamous metaplasia), and lung (minimal bronchioloalveolar epithelial hypertrophy). LOAEL = 0.07

Study Type	Species	Route	Doses (mg/kg/day)	Primary findings
				mg/kg/day.
4-week with 2-week recovery	Beagle Dog	Inhalation	0, 0.03, 0.08, 0.25	Reduced body weight, body weight gain and food intake; absent or slow pupil response to light; corneal opacities; increased heart rate and shortened QT intervals but no change in QTc.  Histopathology changes in the salivary gland (increased weight, acinar hypertrophy and basophilic acini), pharynx (hypertrophy of mucinous acini in the submucosal glands), lacrimal glands (acinar hypertrophy), eyes (occasional corneal ulceration or focal epithelial desquamation), skin of the muzzle (epithelial erosions, scab formation, inflammation, hyperplasia, focal ulceration and hyperkeratosis) and liver (increased incidence of hepatocellular hypertrophy). NOAEL = 0.08 mg/kg/day.
39-week with 4-week recovery	Beagle Dog	Inhalation	0, 0.02, 0.09, 0.27	Reddening of the eyelids or eyes and dry gums; reduced body weight, body weight gain and food intake; ocular discharge, conjunctival hyperemia, faint corneal opacities and corneal ulceration; reduced lacrimal gland secretion; increased heart rate; increased blood urea and phosphorus concentrations.  Histopathology changes in the lacrimal gland (hypertrophy), pharynx, (ectasia of the ducts and/or alveoli, inflammation of the ducts) and salivary gland (hypertrophy of secretory cells). NOAEL = 0.02 mg/kg/day.

NOAEL = No-Observed-Adverse-Effect-Level; LOAEL = Low-Observed-Adverse-Effect-Level

### Genotoxicity

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide.

### Carcinogenicity

Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC) of approximately 53-fold higher in mice and 75-fold higher in rats than the maximum recommended dose of 50 mcg once-daily for humans.

### Reproductive toxicity

SEEBRI® BREEZHALER® was not teratogenic in rats or rabbits following inhalation administration although, significant reductions of maternal food intake and body weights were observed. Furthermore, absence and/or decreased fecal output, thinness, prominent backbone, decreased activity and aborted material/tissue at 0.4 mg/kg/day and 1.3 mg/kg/day were also observed in two rabbits.

Reproduction studies in rats regarding fertility in either males or females or pre- and post-natal development did not reveal many significant events following subcutaneous administration. There were however slight but statistically significant decreases in the number of corpora lutea and implantation sites in females at 1.5 mg/kg/day which were attributed to glycopyrronium bromide. Also, significantly lower pup body weights in the F1 generation (male, female, and genders combined) and growth during the lactation period were seen at 1.5 mg/kg/day.

Diminished rates of conception and of survival at weaning in rats and reduced seminal secretion in dogs have been reported following subcutaneous administration of glycopyrronium bromide at high dose levels.

All these findings were observed at exposures in excess of the maximum human exposure.

Glycopyrronium bromide (including its metabolites) was excreted into the milk of lactating rats.

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**PART III: CONSUMER INFORMATION**Pr **SEEBRI® BREEZHALER®**

Glycopyrronium inhalation powder hard capsules

This leaflet is part III of a three-part "Product Monograph" published when SEEBRI® BREEZHALER® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEEBRI® BREEZHALER®. Contact your doctor, nurse, or pharmacist if you have any questions about the drug.

**PLEASE READ THIS INFORMATION CAREFULLY AND COMPLETELY BEFORE YOU USE SEEBRI® BREEZHALER® EVEN IF YOU HAVE JUST REFILLED YOUR PRESCRIPTION, SINCE SOME INFORMATION MAY HAVE CHANGED.**

**ABOUT THIS MEDICATION****What the medication is used for:**

SEEBRI® BREEZHALER® is used long term once daily to treat breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD).

It is not for treating sudden, severe symptoms of COPD.

**What it does:**

SEEBRI® BREEZHALER® contains glycopyrronium bromide which belongs to a group of medicines called bronchodilators. In COPD the muscles around the airways tighten, making breathing difficult. SEEBRI® BREEZHALER® blocks tightening of these muscles in the lungs, making it easier for air to get in and out of the lungs. When you inhale it, it helps you breathe more easily.

**When it should not be used:**

**Do not use SEEBRI® BREEZHALER®:**

- If you have a severe allergy to glycopyrronium bromide or any other component of SEEBRI® BREEZHALER®. Ask your doctor, nurse, or pharmacist if you are unsure.
- To treat sudden, severe symptoms of COPD such as shortness of breath or wheezing.
- If you have a lactose or severe milk protein allergy as this product contains lactose.
- SEEBRI® BREEZHALER® should not be used in children. COPD does not occur in children.
- If you are younger than 18 years of age.

**What the medicinal ingredient is:**

glycopyrronium bromide.

**What the nonmedicinal ingredients are:**

Lactose monohydrate and magnesium stearate.

The capsule shell contains hypromellose, purified water, carrageenan, potassium chloride and FDC Yellow 6 (110 Sunset Yellow FCF).

**What dosage forms it comes in:**

Clear Orange capsules for oral **inhalation**. Each capsule contains 63 mcg of glycopyrronium bromide equivalent to 50 mcg of glycopyrronium.

Each pack includes an inhaler and capsules (in blister strips) that contain the medicine as inhalation powder.

**WARNINGS AND PRECAUTIONS**

**BEFORE using SEEBRI® BREEZHALER® talk to your doctor, nurse, or pharmacist if you:**

- are pregnant or planning to become pregnant;
- are a breastfeeding mother;
- have heart problems, such as rapid or irregular heart beat or abnormal electrical signal called "prolongation of the QT interval";
- are taking any medications including eye drops, this includes medications you can buy without prescription;
- have an enlarged prostate, problems passing urine or painful urination;
- have eye problems, such as glaucoma or eye pain, blurred vision, see halos around lights or coloured images;
- have any allergies to food or drugs;
- are allergic to lactose (milk sugar);
- have problems with your kidneys.

These capsules are intended for inhalation only.

**DO NOT SWALLOW.**

SEEBRI® BREEZHALER® should not be used more frequently than once daily. Do not exceed the prescribed dose.

This medication has been prescribed for you and should not be given to other people.

Avoid getting the drug powder into your eyes. This may result in eye pain and/or discomfort, temporary blurring of vision, and/or coloured images in association with red eyes. These may be signs of acute narrow-angle glaucoma. Should any of these symptoms develop, consult a doctor immediately.

Remember to tell any other doctor, nurse, dentist or pharmacist you consult that you are taking this medication.

**Driving and Using Machines:**

The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

**During the treatment with SEEBRI® BREEZHALER®, tell your doctor immediately if you experience any of the following symptoms:**

- If you experience a tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation of SEEBRI® BREEZHALER® (signs of bronchospasm)

- If you experience difficulties in breathing or swallowing, swelling of tongue, lips and face, hives or itching, skin rash (signs of hypersensitivity reaction). Do not use **SEEBRI® BREEZHALER®** again before speaking with your doctor.
- If your COPD symptoms (breathlessness, wheezing, cough) do not improve or if they worsen during your treatment stop taking **SEEBRI® BREEZHALER®** and tell your doctor immediately
- if you experience eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes; these may be signs of an acute attack of narrow-angle glaucoma.

**SEEBRI® BREEZHALER® does not relieve sudden symptoms of COPD. Always have a short-acting bronchodilator medicine with you to treat acute symptoms. If you do not have an inhaled, short-acting bronchodilator, contact your healthcare provider to have one prescribed for you.**

**Get emergency medical care if:**

- **breathing problems worsen quickly**
- **you use your short-acting bronchodilator medicine, but it does not relieve your breathing problems**

Ask your doctor or pharmacist for advice before taking any additional medicine.

### INTERACTIONS WITH THIS MEDICATION

Tell your doctor, nurse, or a pharmacist if you are taking or have recently taken any other medicines, including prescription and non-prescription drugs, eye drops, vitamins, and herbal supplements.

It's not recommended to use **SEEBRI® BREEZHALER®** with anticholinergics. Especially tell your doctor if you take any of the following as these medicines may interact with **SEEBRI® BREEZHALER®**:

- atropine or other anticholinergics (ipratropium, oxitropium, tiotropium, etc.).

### PROPER USE OF THIS MEDICATION

Always use this medicine exactly as your doctor, nurse, or pharmacist has told you. Check with your doctor, nurse, or pharmacist if you are not sure.

You can inhale **SEEBRI® BREEZHALER®** before or after food or drink.

#### Usual adult dose:

Inhale the contents of one capsule through the mouth each day, everyday at the same time.

Use **SEEBRI® BREEZHALER®** even when you have no breathing problems or other symptoms of COPD.

You only need to inhale once a day to help you breathe easier because **SEEBRI® BREEZHALER®** lasts for 24 hours. Taking **SEEBRI® BREEZHALER®** at the same time each day will also

help you to remember to use it.

#### How to inhale **SEEBRI® BREEZHALER®**

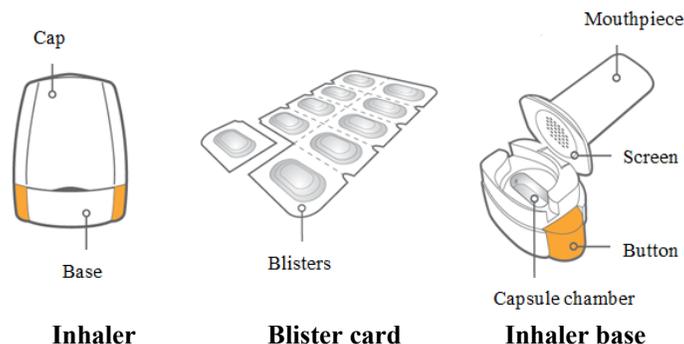
- Only use the inhaler contained in this pack (**SEEBRI® BREEZHALER®** inhaler) to inhale the powder in a capsule. **Do not swallow the capsules.**
- Capsules should always be stored in the blister strip and only removed immediately before use.
- When you start a new pack, use the new **SEEBRI® BREEZHALER®** inhaler supplied in this new pack. Dispose of each inhaler after 30 days of use.

#### How long to continue to take **SEEBRI® BREEZHALER®**

- Keep using **SEEBRI® BREEZHALER®** for as long as your doctor tells you.
- COPD is a long-term disease and you should use **SEEBRI® BREEZHALER®** every day and not only when you have breathing problems or other symptoms of COPD.
- If you have questions about how long to take **SEEBRI® BREEZHALER®**, talk to your doctor or pharmacist.

#### Each one of your **SEEBRI® BREEZHALER®** pack contains

- One **SEEBRI® BREEZHALER®** inhaler consisting of a cap and a base.
- one or more blisters containing **SEEBRI® BREEZHALER®** capsules to be used in the inhaler.



#### Only use the **SEEBRI® BREEZHALER®** inhaler contained in this pack to inhale the powder in the capsule.

Do not use **SEEBRI® BREEZHALER®** capsules with any other inhaler. Do not use **SEEBRI® BREEZHALER®** inhaler to take any other capsule medicine.

Dispose of each inhaler after 30 days. Ask your pharmacist how to dispose of medicines and inhalers no longer required.

**Do not swallow **SEEBRI® BREEZHALER®** capsules.** The powder in the capsules is for you to inhale.

**How to use your SEEBRI® BREEZHALER® inhaler:**

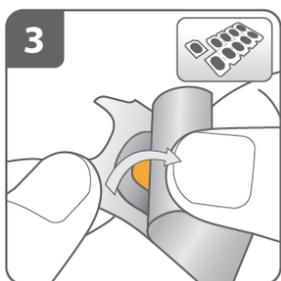


**Pull off cap.**



**Open inhaler:**

Hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler.

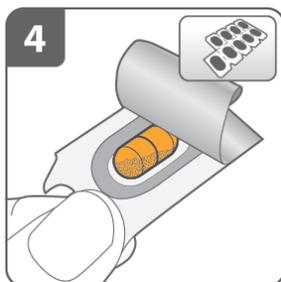


**Prepare capsule:**

Separate one of the blisters from the blister card by tearing along the perforation.

Take one blister and peel away the protective backing to expose the capsule.

Do not push the capsule through the foil.

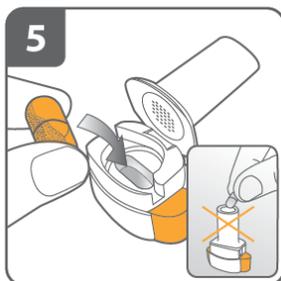


**Remove one SEEBRI® BREEZHALER® capsule:**

Capsules should always be stored in the blister and only removed immediately before use.

With dry hands, remove the capsule from the blister.

Do not swallow the SEEBRI® BREEZHALER® capsule.



**Insert capsule:**

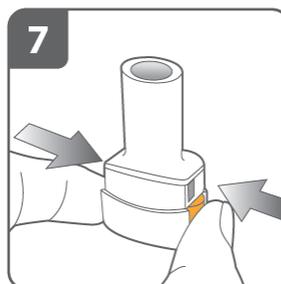
Place the capsule into the capsule chamber.

**Never place a capsule directly into the mouthpiece.**



**Close the inhaler:**

Close the inhaler fully. You should hear a 'click' as it fully closes.

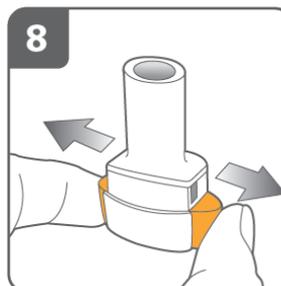


**Pierce the capsule:**

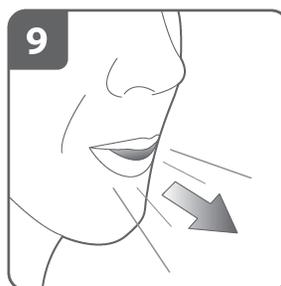
Hold the inhaler upright with the mouthpiece pointing up.

Press both buttons together firmly at the same time. You should hear a 'click' as the capsule is being pierced.

**Do not press the piercing buttons more than once.**



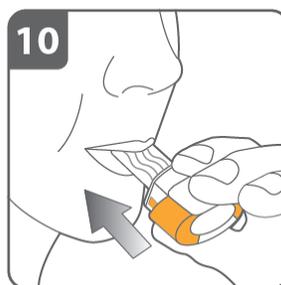
**Release the buttons fully.**



**Breathe out:**

Before placing the mouthpiece in your mouth, breathe out fully.

**Never blow into the mouthpiece.**

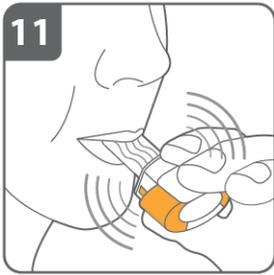


**Inhale the medicine:**

Before breathing in:

- Hold the inhaler as shown in the picture with the buttons to the left and right (not up and down).
- Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece.

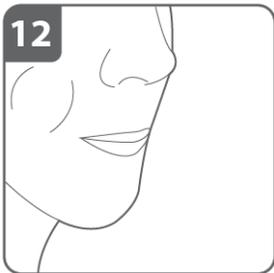
Breathe in rapidly but steadily, as deeply as you can. **Do not press the piercing buttons.**



**Note:**

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet taste as the medicine goes into your lungs.

If you do not hear a whirring noise, the capsule may be stuck in the capsule chamber. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. **Do not press the piercing buttons to loosen the capsule.** Repeat steps 9 and 10 if necessary.

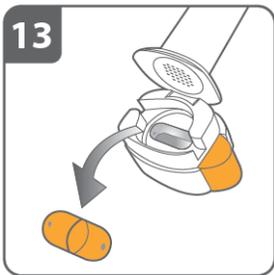


**Hold breath:**

**Continue to hold your breath** for at least 5-10 seconds or as long as comfortably possible while removing the inhaler from your mouth. Then breathe out.

Open the inhaler to see if any powder is left in the capsule. **If there is powder left in the capsule**, close the inhaler and repeat steps 9 to 12. Most people are able to empty the capsule with one or two inhalations.

Some people occasionally cough briefly soon after inhaling the medicine. If you do, don't worry, as long as the capsule is empty, you have received the full dose.



**Remove capsule:**

**After you have finished taking** your daily dose of SEEBRI® BREEZHALER®, open the mouthpiece again, remove the empty capsule by tipping it out of the capsule chamber, and discard it. Close the inhaler and replace the cap.

**Do not store the capsules in the SEEBRI® BREEZHALER® inhaler.**

**REMEMBER:**

- **Do not swallow SEEBRI® BREEZHALER® capsules.**
- **Only use the SEEBRI® BREEZHALER® inhaler contained in this pack.**
- SEEBRI® BREEZHALER® capsules must always be stored in the blister, and only removed immediately before use.
- Never place a SEEBRI® BREEZHALER® capsule directly into the mouthpiece of the SEEBRI® BREEZHALER® inhaler.

- Do not press the piercing buttons more than once.
- Never blow into the mouthpiece of the SEEBRI® BREEZHALER® inhaler.
- Always release the push buttons before inhalation.
- Never wash the SEEBRI® BREEZHALER® inhaler with water. Keep it dry. See below **“How to clean your inhaler”**.
- Never take the SEEBRI® BREEZHALER® inhaler apart.
- Always keep the SEEBRI® BREEZHALER® inhaler and SEEBRI® BREEZHALER® capsules in a dry place.
- Avoid getting the drug powder in your eyes.

**Additional information**

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is pierced more than once (step 7).

**How to clean your inhaler**

Never wash your inhaler with water. If you want to clean your inhaler, wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry.

**Overdose:**

**If you think you have inhaled too much SEEBRI® BREEZHALER®, contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.**

**Missed Dose:**

If you forget to inhale a dose, inhale one as soon as possible but do not inhale two doses on the same day. Then inhale the next dose as usual.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

As with all medicines, patients using SEEBRI® BREEZHALER® may experience side effects, although not everybody gets them.

Side effects may include:

- Upset stomach, indigestion
- Pain in extremities (e.g. arms or legs)
- Feeling of pressure or pain in the cheeks and forehead (possible symptoms of sinus congestion)
- Dry mouth
- Nausea, vomiting, diarrhea and abdominal pain (possible symptoms of gastroenteritis)
- Difficulty sleeping

- Symptoms of common cold (runny or stuffy nose, cough, sore throat, sneezing)
- Pain in muscles, bones or joints
- Cavities
- Rash
- Tiredness
- Weakness
- Throat irritation
- Nose bleeds
- Tingling or numbness
- Itching
- Voice alteration (hoarseness)

Some elderly patients above 75 years of age have also experienced headache and urinary tract infection.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate emergency medical help
		Only if severe	In all cases	
Uncommon	New occurrence of irregular heart beat			✓
	<b>Increased blood sugar:</b> Frequent urination, thirst, and hunger		✓	
	Difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips		✓	
	<b>Glaucoma:</b> New or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos of bright colours around lights, red eyes			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate emergency medical help
		Only if severe	In all cases	
Unknown	<b>Paradoxical Bronchospasm:</b> Tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation of SEEBRI® BREEZHALER®			✓
	<b>Allergic Reaction:</b> rash, hives, swelling of the face, mouth, lips, throat and tongue, difficulty swallowing or breathing			✓

*This is not a complete list of side effects. For any unexpected effects while taking SEEBRI® BREEZHALER®, contact your doctor, nurse, or pharmacist.*

#### HOW TO STORE IT

Do not use after the expiry date shown on the box.

Store SEEBRI® BREEZHALER® at room temperature between 15 to 25°C.

Store the capsules in the original package in a dry place in order to protect from heat and moisture. Do not remove capsules from the blister pack until immediately before use.

Do not use this medicine if you notice that the pack is damaged or show signs of tampering.

Each inhaler should be disposed of after 30 days of use.

Keep out of sight and reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the product monograph, prepared for health professionals can be found at: <http://www.novartis.ca>

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883

This leaflet was prepared by:  
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