PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSEEBRI® BREEZHALER®

Glycopyrronium inhalation powder

inhalation powder hard capsules, 50 mcg glycopyrronium as glycopyrronium bromide per capsule
oral inhalation

Inhaled Bronchodilator (Long-Acting Muscarinic Antagonist (LAMA))

SEEBRI® BREEZHALER® capsules to be used only with the supplied
SEEBRI® BREEZHALER® inhalation device

Novartis Pharmaceuticals Canada Inc.
700 Saint-Hubert St., Suite 100
Montreal, Quebec
H2Y 0C1

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RECENT MAJOR LABEL CHANGES

No recent major label changes within the last 24 months.	

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (< 18 years of age): SEEBRI BREEZHALER should not be used in patients under 18 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): SEEBRI BREEZHALER can be used at the recommended dose in elderly patients 65 years of age and older.

2 CONTRAINDICATIONS

SEEBRI BREEZHALER (glycopyrronium bromide) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with severe hypersensitivity to milk proteins.

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 Recommended Dose and Dosage Adjustment

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 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Hepatic impairment

No specific studies have been conducted in patients with hepatic impairment. SEEBRI BREEZHALER 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 BREEZHALER can be used at the recommended dose in elderly patients 65 years of age and older.

Pediatric patients

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

4.4 Administration

SEEBRI BREEZHALER is recommended for once-daily administration at the same time each day.

SEEBRI BREEZHALER capsules must be administered only by the oral inhalation route and only using the SEEBRI BREEZHALER inhaler. SEEBRI BREEZHALER capsules must not be swallowed (see also 5 OVERDOSAGE).

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

When prescribing SEEBRI BREEZHALER, 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.

4.5 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.

5 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 BREEZHALER at total doses of 100 and 200 mcg once-daily for 28 days were well tolerated.

Acute intoxication by inadvertent oral ingestion of SEEBRI BREEZHALER 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral inhalation	Inhalation powder hard capsules/ contain 50 mcg glycopyrronium as glycopyrronium bromide	Carrageenan, FDC Yellow 6 (110 Sunset Yellow FCF), hypromellose, lactose monohydrate, magnesium stearate, potassium chloride, and purified water.

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

The following pack types are available:

- Carton of 30 SEEBRI BREEZHALER capsules (3 blister cards) and one SEEBRI BREEZHALER device.
- Carton of 2 SEEBRI BREEZHALER capsules (1 blister card) and one SEEBRI BREEZHALER device.

7 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 beta2-agonist becomes less effective or the patient needs more inhalation of short-acting beta2-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.

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.

Driving and Operating Machinery

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. Hence, exercise caution when driving or operating a vehicle or potentially dangerous machinery.

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^2) including those with end-stage renal disease requiring dialysis, SEEBRI BREEZHALER should be used only if the expected benefit outweighs the potential risk (see 10 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 BREEZHALER may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, SEEBRI BREEZHALER should be discontinued immediately and alternative therapy instituted.

7.1 Special Populations

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

7.1.1 Pregnant Women

There are no data available on the use of SEEBRI BREEZHALER in pregnant women. Therefore, SEEBRI BREEZHALER should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

7.1.2 Breast-feeding

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 16 NON-CLINICAL TOXICOLOGY). The use of SEEBRI BREEZHALER by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

7.1.3 Pediatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety and tolerability of SEEBRI BREEZHALER 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2). Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.

Table 2 - Adverse drug reactions ≥1.0% in pooled COPD safety database

COPD 6-month safety database		
Adverse drug reactions	**Glycopyrronium bromide 50mcg once daily n=1075[1] N (%)[2]**	**Placebo n=535[1] N (%)[2]**
Gastrointestinal disorders		
- Dry mouth	26 (2.4)	6 (1.1)

- Gastroenteritis	15 (1.4)	5 (0.9)
Psychiatric disorders		
- Insomnia	11 (1.0)	4 (0.8)

COPD 12-month safety database		
	n=525 N (%)	**n=268 N (%)**
Infections and infestations		
- Nasopharyngitis	47 (9.0)	15 (5.6)
- Rhinitis	9 (1.7)	2 (0.7)
Gastrointestinal disorders		
- 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)
Musculoskeletal and connective tissue disorders		
- 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)
Cardiac disorders		
- Atrial fibrillation	7 (1.3)	2 (0.7)
Renal and urinary tract disorders		
- Dysuria	6 (1.1)	0
Metabolism and nutrition disorders		
- Hyperglycemia	6 (1.1)	2 (0.7)
Respiratory, thoracic and mediastinal disorders		
- Sinus congestion	6 (1.1)	2 (0.7)

[1] n= number of patients analysed
[2] 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.

8.3 Less Common Clinical Trial Adverse Reactions

The following clinical trial adverse reactions were reported in less than 1% of patients:

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.

8.5 Post-Market Adverse 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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

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. *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. Metabolism in which multiple enzymes are involved plays a secondary role in the elimination of glycopyrronium (see 10 CLINICAL PHARMACOLOGY). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

9.4 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.

Table 3 - Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical Comment
cimetidine	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: CT = Clinical Trial

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Elimination). Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide provides further evidence for this.

10.2 Pharmacodynamics

Primary Pharmacodynamic Effects

SEEBRI BREEZHALER increased trough FEV_1 (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_1 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_1 relative to baseline ranging from 0.091 L to 0.094 L.

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 (≤ 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 (≤ 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.

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_{max}) about 50-fold higher than after inhalation of SEEBRI BREEZHALER 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 BREEZHALER 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 BREEZHALER 200 mcg in COPD patients.

10.3 Pharmacokinetics

Table 4 - Summary of SEEBRI BREEZHALER's Pharmacokinetic Parameters in COPD patients

Mean (Standard Deviation)	C_{max} [pg/mL]	T½ (h)	AUC_{0-24h} [pg*h/mL]	Renal Clearance (CLr) [L/h]	Volume of distribution (Vss) [3] [L]
Single dose	146 (109)	52.5 (12.7) [1]	n.d.	23.1 (7.46) [1]	82.7 (21.7) [1]
Multiple dose (steady state)	166 (97.3)	13.4 (8.02) [2] 20.8 (8.61) [2] 21.6 (3.24) [2]	464 (213)	17.6 (6.4)	n.d.
Notes: n.d.= not determined; [1] Determined in a biopharmaceutical study in healthy volunteers; [2] Determined in a pharmacokinetic study in COPD patients for doses of 50, 100 and 200 mcg respectively [3] Steady-state volume of distribution (Vss), determined in a biopharmaceutical study in healthy volunteers					

Absorption

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

The absolute bioavailability of glycopyrronium inhaled via SEEBRI BREEZHALER 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 (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/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. ≤ 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.

Elimination

After i.v. administration of [^{3}H]-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.

Gender, smoking status and baseline FEV_1 had no apparent effect on systemic exposure.

- **Pediatrics:** SEEBRI BREEZHALER should not be used in patients under 18 years of age.
- **Geriatrics:** Dose adjustment is not necessary for patients aged 65 years and older.
- **Ethnic Origin:** 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 (CLr) 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.
- **Hepatic Insufficiency:** 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.

- **Renal Insufficiency:** Renal impairment has an impact on the systemic exposure to glycopyrronium. A moderate mean increase in total systemic exposure (AUC_{last}) 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≥30 mL/min/1.73m2), SEEBRI BREEZHALER can be used at the recommended dose. There is no long term experience in patients with renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

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

Keep out of the reach of children.

12 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.

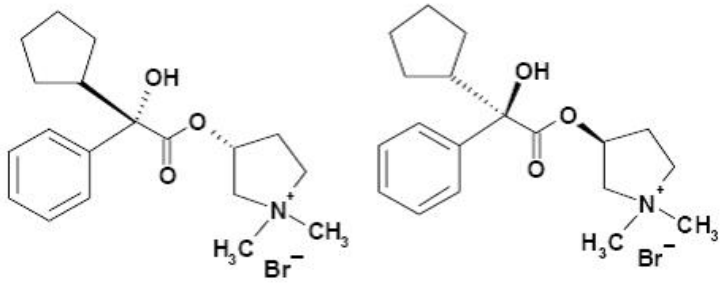
PART II: SCIENTIFIC INFORMATION

13 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:	C19H28NO3 Br Salt form on anhydrous basis: 398.33

Structural formula:



[2S, 3R]-stereoisomer [2R, 3S]-stereoisomer

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 BREEZHALER INHALATION DEVICE

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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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_1 <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV_1/FVC ratio of less than 70%.

Assessment of efficacy in trials A2304 and A2303 was based on FEV_1. The primary efficacy endpoint was 24-hour post-dose trough FEV_1 (defined as the average of two FEV_1 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_1 , FVC and IC assessed at various time points over the treatment period.

Table 5 - Summary of patient demographics for clinical trials in COPD

Study #	Trial design and dosage	Route of administration and duration	Study subjects‡ (n=number)	Mean age (Range)	Gender
A2303	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	Glycopyrronium Inhalation 52 weeks	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	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	glycopyrronium Inhalation 26 weeks	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

14.2 Study Results

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_1 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_1 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_1 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_1 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_1 standardized (for time) area under the curve (AUC). In the 6-month study, FEV_1 $AUC_{0\text{-}24h}$ 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_1 $AUC_{0\text{-}24h}$ 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_1 (L)) after first dose

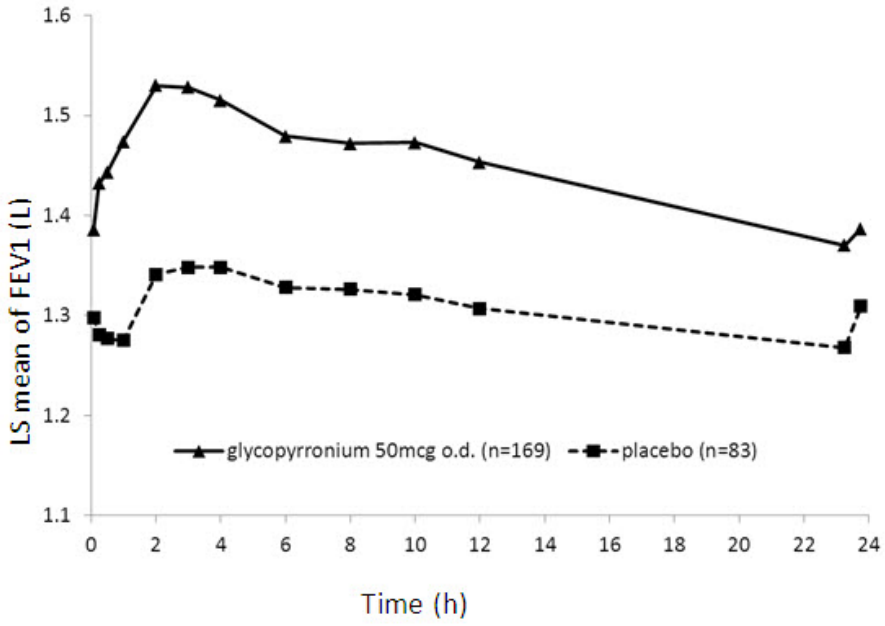


Figure 2 - Six-month pivotal study: Serial spirometry data (least square means of FEV_1 (L)) at week 12

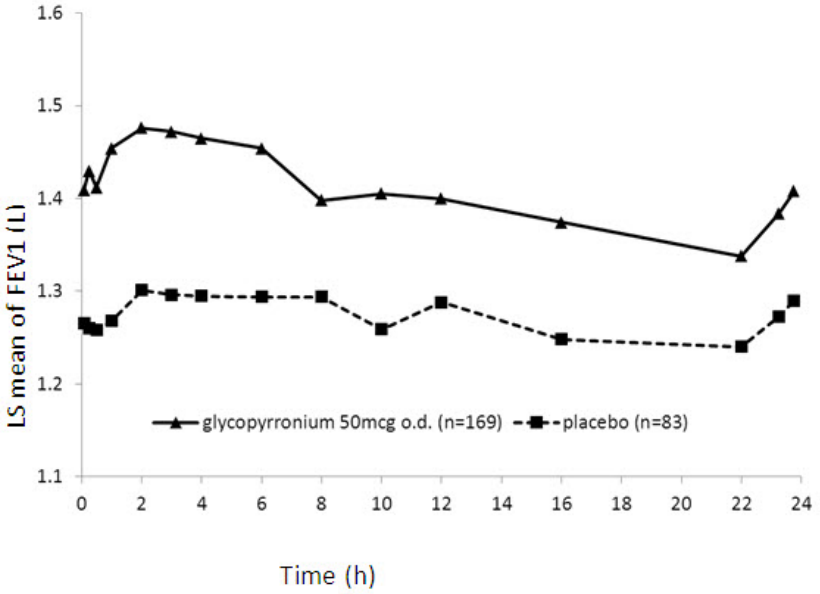


Figure 3 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV1 (L)) after first dose

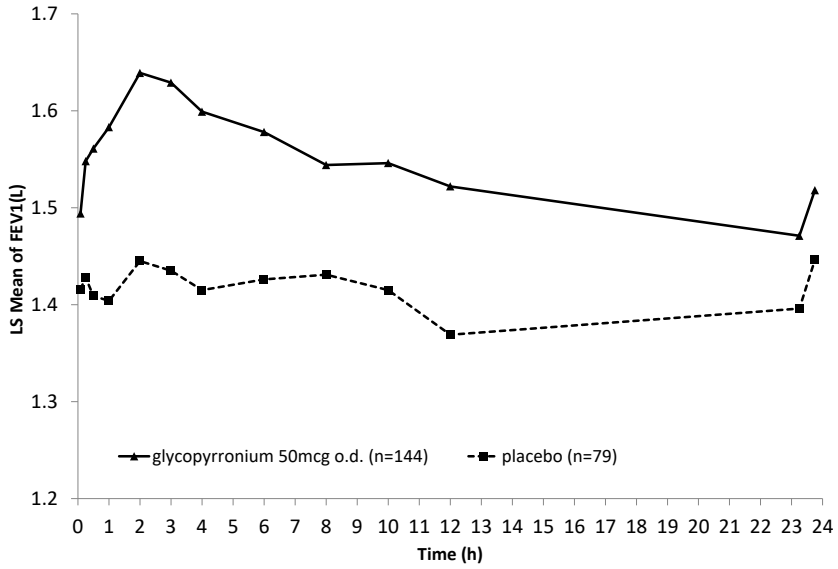


Figure 4 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV1 (L)) at week 12

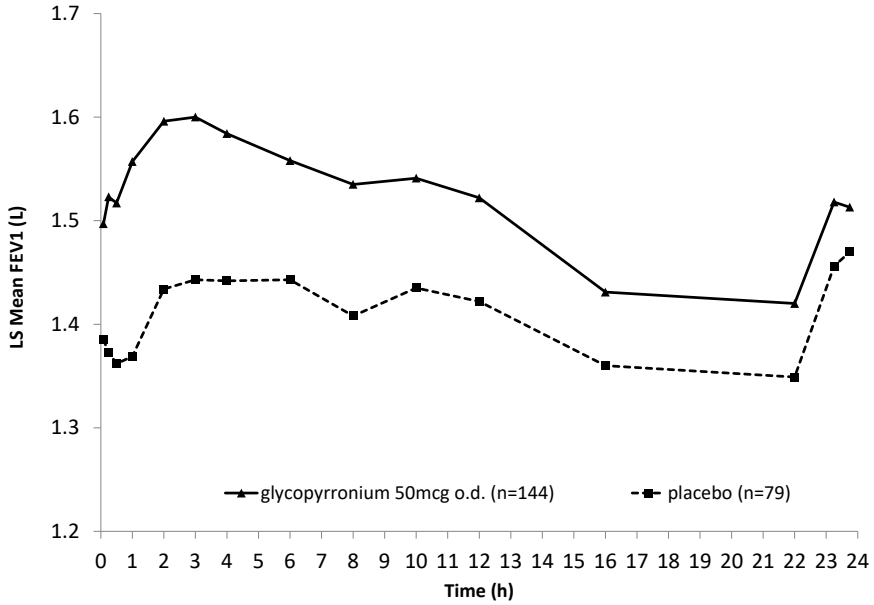
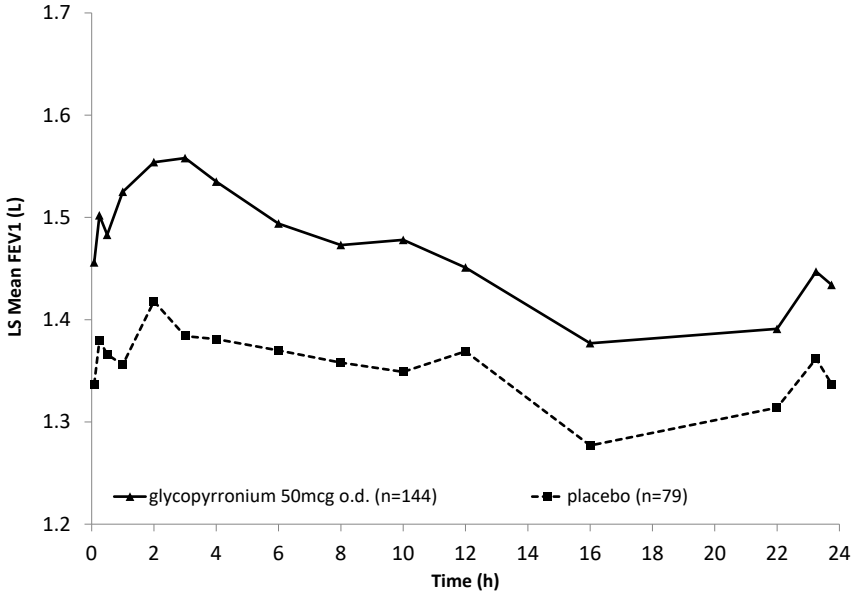


Figure 5 - Twelve-month pivotal study: Serial spirometry data (least square means of FEV1 (L)) at week 52



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 ($p\leq0.001$) 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 6) and 12 month (Table 7) phase III pivotal studies.

Table 6 – 6 Month pivotal study data

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

			Baseline	Treatment	SEEBRI BREEZHALER 50 mcg o.d. v.s. placebo -Treatment difference-		
Endpoint	**Treatment**	**n**	**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

			SEEBRI BREEZHALER 50 mcg o.d. v.s. place		
Endpoint	**Treatment**	**n / N' (%)**	**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 7 – 12 Month pivotal study data

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

			Baseline	Treatment	SEEBRI BREEZHALER 50 mcg o.d. v.s. placebo -Treatment difference-		
Endpoint	**Treatment**	**n**	**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

			SEEBRI BREEZHALER 50 mcg o.d. v.s. placebo		
Endpoint	**Treatment**	**n / N' (%)**	**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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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. 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

Repeat dose inhalation toxicity studies were conducted in rats (up to 26 weeks) and dogs (up to 39 weeks). The effects observed in the repeated-dose studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium or mild local irritation in the upper respiratory tract or adaptive response. A transient mild to moderate increases in heart rate in dogs, mydriasis in rats and a number of reversible changes including reduced secretions from the salivary and lacrimal glands in dogs and associated morphological changes in these glands and pharynx, and histopathological changes in Harderian glands in rats were related to exaggerated pharmacological effect of glycopyrronium. 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 in the upper respiratory tract. 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 at the therapeutic dose.

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.

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

Reproductive and Developmental Toxicology:

Glycopyrronium bromide 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSEEBRI® BREEZHALER®

Glycopyrronium inhalation powder hard capsules

Read this carefully before you start taking **SEEBRI® BREEZHALER®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SEEBRI BREEZHALER.**

What is SEEBRI BREEZHALER used for?

- SEEBRI BREEZHALER is used long term in adults to manage airway blockage from chronic obstructive pulmonary disease (COPD; a lung disease that makes it hard to breathe). This can include chronic bronchitis (inflammation of the lungs) and emphysema (damage to parts of the lung known as alveoli).
- SEEBRI BREEZHALER is **not** a rescue medicine and should **not** be used on an as needed basis for treating sudden, severe symptoms of COPD (e.g. sudden breathing problems). Your healthcare professional may give you other medicines to use for sudden breathing problems.

How does SEEBRI BREEZHALER work?

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.

What are the ingredients in SEEBRI BREEZHALER?

Medicinal ingredient: glycopyrronium bromide

Non-medicinal ingredients: carrageenan, FDC Yellow 6 (110 Sunset Yellow FCF), hypromellose, lactose monohydrate (which contains milk protein), magnesium stearate, potassium chloride, purified water

SEEBRI BREEZHALER comes in the following dosage forms:

Inhalation powder hard capsules: 50 mcg of glycopyrronium (as glycopyrronium bromide)

Do not use SEEBRI BREEZHALER if:

- you are allergic to glycopyrronium bromide or any of the other ingredients in SEEBRI BREEZHALER (see **What are the ingredients in SEEBRI BREEZHALER?**)
- you have a severe milk protein allergy as SEEBRI BREEZHALER contains lactose

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SEEBRI BREEZHALER. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning to become pregnant
- are breastfeeding or plan to breastfeed
- have or have had heart problems, such as rapid or irregular heartbeat or long QT syndrome

- are taking any medications including eye drops, this includes medications you can buy without prescription
- have difficulty urinating, which can include problems caused by an enlarged prostate
- have eye pain caused by increased pressure in the eyes (narrow-angle glaucoma)
- have kidney problems

Other warnings you should know about:

Eye problems: Avoid getting SEEBRI BREEZHALER powder into your eyes. This may cause eye pain, discomfort, temporary blurring of vision, and/or coloured images in association with red eyes. These may be signs of acute narrow-angle glaucoma (eye pain caused by increased pressure in the eyes). If you develop any of these symptoms, talk to your healthcare professional right away.

Driving and Using Machines: SEEBRI BREEZHALER can cause dizziness or blurred vision. You should not drive or operate machinery if this occurs.

Monitoring: Your healthcare professional might monitor your health throughout your treatment with SEEBRI BREEZHALER. This can include monitoring your kidneys and the development of sudden or worsening COPD symptoms.

Talk to your healthcare professional immediately if:

- your shortness of breath becomes worse
- you don't get the same benefit from your medicine as you did before
- you have breathing difficulties and chest pain
- you have trouble urinating

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SEEBRI BREEZHALER:

- medicines similar to SEEBRI BREEZHALER (other short- or long-acting muscarinic antagonists) used for your lung disease. They may interact with SEEBRI BREEZHAER and increase the risk of experiencing side effects.

How to take SEEBRI BREEZHALER:

- SEEBRI BREEZHALER has been prescribed for you and should not be given to other people. Take SEEBRI BREEZHALER capsules exactly as your healthcare professional has told you. Do not take more than once a day or exceed the prescribed dose. You should check with your healthcare professional if you are not sure.
- Your healthcare professional may also provide you with an inhaled short-acting bronchodilator for the treatment of COPD symptoms that may occur suddenly.
- The contents of the capsule must be inhaled once daily through the mouthpiece of the SEEBRI BREEZHALER inhlation device only. **Do NOT swallow the capsule.** The SEEBRI BREEZHALER

inhaler is especially designed for SEEBRI BREEZHALER capsules and must **not** be used with any other capsules. Likewise, you should not take your SEEBRI BREEZHALER capsules with any inhalation device other than the SEEBRI BREEZHALER inhaler.

- When you start a new pack, use the new SEEBRI BREEZHALER inhaler supplied in the new pack. Dispose of each inhaler after 30 days of use.
- You can inhale SEEBRI BREEZHALER before or after food or drink.
- Store the SEEBRI BREEZHALER capsules in the blister strip until immediately before use.
- Before starting your treatment with SEEBRI BREEZHALER, make sure that you are completely familiar with the use and proper care of the SEEBRI BREEZHALER inhaler. See the **Instructions for Use** for complete information.
- It is important that you continue to take SEEBRI BREEZHALER regularly even if you feel fine and do not have any symptoms.

If you have any questions about SEEBRI BREEZHALER or the SEEBRI BREEZHALER inhaler, talk to your healthcare professional.

Usual dose:

One (1) SEEBRI BREEZHALER capsule is to be inhaled once daily, preferably at the same time each day, only with the SEEBRI BREEZHALER inhaler.

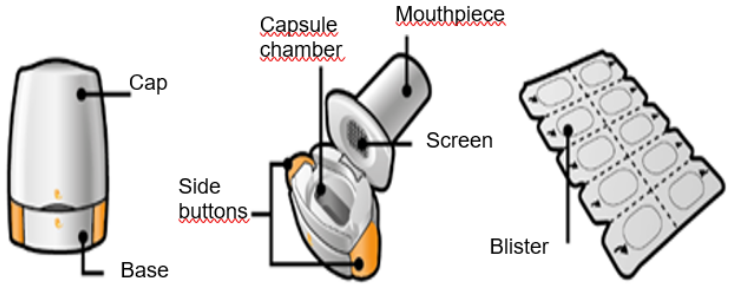
Instructions for Use

This part of the leaflet explains how to use and care for your SEEBRI BREEZHALER inhaler. Please read carefully and follow these instructions.

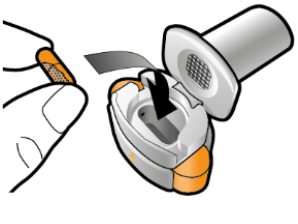
If you have any questions, ask your healthcare professional.

Your SEEBRI BREEZHALER Inhaler pack contains:

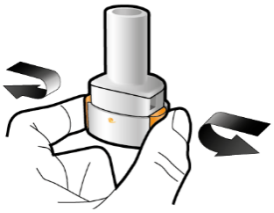
- One SEEBRI BREEZHALER inhaler
- One or more blister cards containing the SEEBRI BREEZHALER capsules to be used in the inhaler



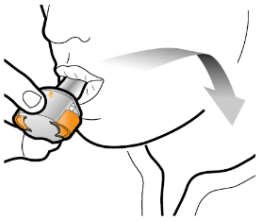
Please read the full "Instructions for Use" before using the SEEBRI BREEZHALER Inhaler.



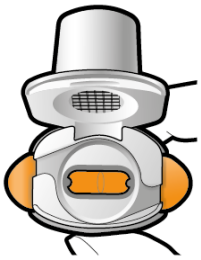
Insert



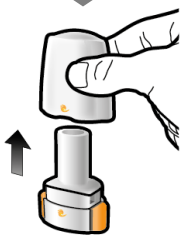
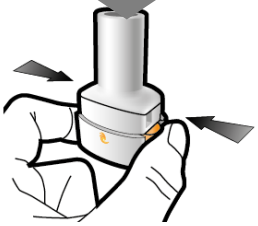
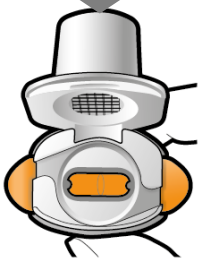
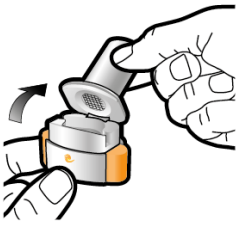
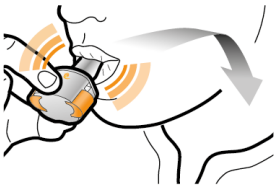
Pierce and release



Inhale deeply



Check capsule is empty

1	2	3	Check
			
Step 1a: **Pull off cap**	Step 2a: **Pierce capsule once** Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced. Only pierce the capsule once.	Step 3a: **Breathe out fully** Do not blow into the inhaler.	**Check capsule is empty** Open the inhaler to see if any powder is left in the capsule.
			If there is powder left in the capsule: • Close the inhaler. • Repeat steps 3a to 3c.

Step 1b:

Open inhaler

Step 1c:

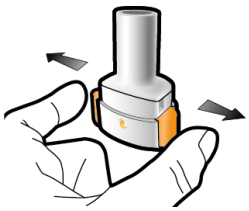
Remove capsule

Separate one of the blisters from the blister card.

Peel open the blister and remove the capsule.

Do not push the capsule through the foil.

Do not swallow the capsule.



Step 2b:

Release side buttons

Step 3b:

Inhale medicine deeply

Hold the inhaler as shown in the picture.

Place the mouthpiece in your mouth and close your lips firmly around it.

<u>Do not press the side buttons.</u>

Breathe in quickly and as deeply as you can.

During inhalation, you will hear a whirring noise.

You may taste the medicine as you inhale.

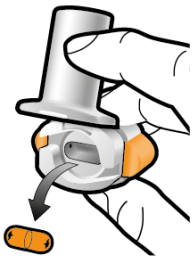
Step 3c:

Hold breath

Hold your breath for up to 5 seconds.

Powder remaining

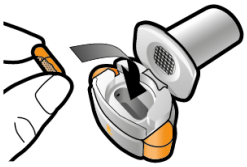
Empty



Remove empty capsule

Put the empty capsule in your household waste.

Close the inhaler and replace the cap.

 Step 1d: **Insert capsule** Never place a capsule directly into the mouthpiece.  Step 1e: **Close inhaler**			**Important Information** • SEEBRI BREEZHALER capsules must always be stored in the blister card and only removed immediately before use. • Do not push the capsule through the foil to remove it from the blister. • Do not swallow the capsule. • Do not use the SEEBRI BREEZHALER capsules with any other inhaler. • Do not use the SEEBRI BREEZHALER inhaler to take any other capsule medicine. • Never place the capsule into your mouth or the mouthpiece of the inhaler. • Do not press the side buttons more than once. • Do not blow into the mouthpiece. • Do not press the side buttons while inhaling through the mouthpiece. • Do not handle capsules with wet hands. • Never wash your inhaler with water.

Frequently Asked Questions	Cleaning the inhaler
Why didn't the inhaler make a noise when I inhaled? The capsule may be stuck in the capsule chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3c. **What should I do if there is powder left inside the capsule?** You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3c. **I coughed after inhaling – does this matter?** This may happen. As long as the capsule is empty you have received enough of your medicine. **I felt small pieces of the capsule on my tongue – does this matter?** This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.	Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry. Never wash your inhaler with water. **Disposing of the inhaler after use** Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

Overdose:

If you think you, or a person you are caring for, have inhaled too much SEEBRI BREEZEHALER, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose with SEEBRI BREEZHALER include:

- constipation
- difficulty urinating
- increased eye pressure or pain
- eye redness
- vision changes

Missed Dose:

If you miss or forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regularly scheduled time. Do not take two doses at the same time on the same day.

What are possible side effects from using SEEBRI BREEZEHALER?

These are not all the possible side effects you may have when taking SEEBRI BREEZEHALER. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- cough
- hoarse voice
- headache
- upset stomach, indigestion
- vomiting
- feeling of pressure or pain in the cheeks and forehead (sinus congestion)
- runny or stuffy nose, sore throat
- dry mouth or throat. Talk to your healthcare professional if the dry mouth persists.
- difficulty sleeping (insomnia)
- fatigue, weakness
- pain in muscles, bones or joints, pain in arms or legs
- tingling or numbness
- dental cavities
- rash, itching
- nose bleeds

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Heart palpitations: unusually fast or irregular heartbeat		✓	
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Urinary retention (inability to pass urine or to empty the bladder): difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips		✓	
Eye problems: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos of bright colours around lights, red eyes			✓
Gastroenteritis (inflammation of the stomach and intestines): abdominal pain, diarrhea, results in nausea, vomiting		✓	
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Paradoxical bronchospasm (sudden narrowing of the airways after taking medicines known as bronchodilators): tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation of SEEBRI BREEZHALER			✓
Allergic reaction: rash, hives, swelling of the face, mouth, lips, throat and tongue, difficulty swallowing or breathing			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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 reach and sight of children.

If you want more information about SEEBRI BREEZHALER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novartis.ca), Novartis Pharmaceuticals Canada Inc., or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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