NOVARTIS

Seebri® Breezhaler®

Long-acting muscarinic antagonist.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

50 microgram glycopyrronium, inhalation powder hard capsules.

Transparent orange capsules containing a white powder, with the product code GPL50 printed in black above a black bar and the company logo ( ) printed under a black bar.

Active substance

Each capsule contains 63 microgram glycopyrronium bromide equivalent to 50 microgram glycopyrronium.

The delivered dose (the dose that leaves the mouthpiece of the Seebri Breezhaler inhaler) contains 55 microgram glycopyrronium bromide equivalent to 44 microgram glycopyrronium.

Active Moiety

Glycopyrronium.

Excipients

Capsule fill: Lactose monohydrate, magnesium stearate.

Capsule shell components: Hypromellose, purified water, carrageenan, potassium chloride, FDC Yellow 6 (110 Sunset Yellow FCF).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Seebri Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION

General target population

The recommended dosage of Seebri Breezhaler is the once-daily inhalation of the content of one 50 microgram capsule using the Seebri Breezhaler inhaler.

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 sections WARNINGS AND PRECAUTIONS and 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 75 years of age and older.

Pediatric patients

Seebri Breezhaler should not be used in patients under 18 years of age.

Method of administration

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 section OVERDOSAGE).

Seebri Breezhaler is recommended to be administered once-daily at the same time of the day each day. 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.

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 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.

CONTRAINDICATIONS

Seebri Breezhaler is contraindicated in patients with hypersensitivity to glycopyrronium or to any of the excipients of the preparations (see sections DESCRIPTION AND COMPOSITION and WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

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.

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.

Paradoxical bronchospasm

As with other inhalation therapy, 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.

Anticholinergic effect

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

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Seebri Breezhaler and to contact their doctor immediately should any of these signs or symptoms develop.

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 section CLINICAL PHARMACOLOGY). These patients should be monitored closely for potential adverse drug reactions.

Patients with a history of cardiovascular disease

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 (Fridericia method) was prolonged (>450 ms for males or >470 ms for females) were excluded from the clinical trials, and therefore the experience in these patient groups is limited. Seebri Breezhaler should be used with caution in these patient groups.

Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

ADVERSE DRUG REACTIONS

Summary of the safety profile

The safety and tolerability of Seebri Breezhaler has been explored at the recommended dose of 50 µg once-daily in 1353 COPD patients. Of these, 842 patients have been treated for at least 26 weeks, and 351 patients for at least 52 weeks.

The safety profile is characterized by symptoms related to anticholinergic effects. Adverse drug reactions related to local tolerability included throat irritation, nasopharyngitis, rhinitis and sinusitis.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions 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. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).

Table 1 Adverse drug reactions in pooled COPD safety database

Adverse drug reactions	Glycopyrronium bromide 50µg once daily n=1075 N (%)	Placebo n=535 N (%)	Frequency category
Gastrointestinal disorders			
- Dry mouth	26 (2.4)	6 (1.1)	common
- Gastroenteritis	15 (1.4)	5 (0.9)	common
- Dyspepsia	8 (0.7)	2 (0.4)	uncommon
- Dental caries	4 (0.4)	0 (0)	uncommon
Psychiatric disorders			
- Insomnia	11 (1.0)	4 (0.8)	common
Musculoskeletal and connective tissue disorders			
- Pain in extremity	10 (0.9)	1 (0.2)	uncommon
- Musculoskeletal chest pain	8 (0.7)	3 (0.6)	uncommon
Skin and subcutaneous tissue disorders			
- Rash	10 (0.9)	2 (0.4)	uncommon
General disorders and administration site conditions			
- Fatigue	9 (0.8)	3 (0.6)	uncommon
- Asthenia	8 (0.7)	2 (0.4)	uncommon
Respiratory, thoracic and mediastinal disorders			
- Sinus congestion	8 (0.7)	2 (0.4)	uncommon
- Productive cough	7 (0.7)	1 (0.2)	uncommon
- Throat irritation	6 (0.6)	1 (0.2)	uncommon
- Epistaxis	3 (0.3)	1 (0.2)	uncommon
Infections and infestations			
- Rhinitis	8 (0.7)	2 (0.4)	uncommon
- Cystitis	3 (0.3)	0 (0)	uncommon

Adverse drug reactions	Glycopyrronium bromide 50µg once daily n=1075 N (%)	Placebo n=535 N (%)	Frequency category
Metabolism and nutrition disorders			
- Hyperglycemia	8 (0.7)	2 (0.4)	uncommon
Renal and urinary disorders			
- Dysuria	7 (0.7)	1 (0.2)	uncommon
- Urinary retention	2 (0.2)	0 (0)	uncommon
Cardiac disorders			
- Atrial fibrillation	6 (0.6)	0 (0)	uncommon
- Palpitations	2 (0.2)	0 (0)	uncommon
Nervous system disorders			
- Hypoesthesia	6 (0.6)	0 (0)	uncommon

In the 12-month study the following additional adverse drug reactions were more frequent on Seebri Breezhaler than on placebo: nasopharyngitis (9.0 vs 5.6%), vomiting (1.3 vs 0.7%), musculoskeletal pain (1.1 vs 0.7%), neck pain (1.3 vs 0.7%), diabetes mellitus (0.8 vs 0%).

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

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 possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports (frequency not known)

Immune system disorders

Angioedema; hypersensitivity

Respiratory, thoracic and mediastinal disorders

Paradoxical bronchospasm; dysphonia

Skin and subcutaneous tissue disorders

Pruritus

Description of selected adverse drug reactions

The most common anticholinergic adverse 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.

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.

INTERACTIONS

The co-administration of Seebri Breezhaler with inhaled anticholinergic-containing drugs has not been studied and is therefore, like for other anticholinergics, not recommended.

Concomitant administration of Seebri Breezhaler and orally inhaled indacaterol, a beta2-adrenergic agonist, under steady-state conditions of both drugs did not affect the pharmacokinetics of either drug.

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 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 transport.

In vitro studies showed that Seebri Breezhaler is not likely to inhibit or induce the metabolism of other drugs, nor processes involving drug transporters. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see section CLINICAL PHARMACOLOGY – Biotransformation/metabolism and Elimination). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential

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

Pregnancy

No clinical data on exposed pregnancies in COPD patients are available. Seebri Breezhaler

was not teratogenic in rats or rabbits following inhalational administration (see section NON-CLINICAL SAFETY DATA). In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, umbilical plasma concentrations were low. As there is no adequate experience in pregnant women, Seebri Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Breast-feeding

It is not known whether glycopyrronium bromide passes into human breast milk. However, glycopyrronium bromide (including its metabolites) was excreted into the milk of lactating rats. 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. See section NON-CLINICAL SAFETY DATA.

Fertility

Reproduction studies and other data in animals did not indicate a concern regarding fertility in either males or females (see section NON-CLINICAL SAFETY DATA).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Glycopyrronium has no or negligible influence on the ability to drive and use machines

OVERDOSAGE

High doses of glycopyrronium may lead to anticholinergic signs and symptoms for which symptomatic treatment may be indicated.

In COPD patients, repeated orally inhaled administration of Seebri Breezhaler at total doses of 100 and 200 µg 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 i.v. administration of 150 µg glycopyrronium bromide (equivalent to 120 µg glycopyrronium) in healthy volunteers were respectively about 50-fold and 6-fold higher than the peak and total systemic exposure at steady-state achieved with the recommended dose (50 µg once-daily) of Seebri Breezhaler and were well tolerated.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Drugs for obstructive airway diseases, anticholinergics, ATC code: R03BB06

Mechanism of action (MOA)

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 bromide 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 section CLINICAL PHARMACOLOGY – Elimination). Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide provides further evidence for this.

Pharmacodynamics (PD)

Primary Pharmacodynamic Effects

Seebri Breezhaler provided consistently significant improvement in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours in a number of clinical pharmacodynamic and efficacy trials.

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. During the first 4 hours after drug administration bronchodilation was significantly greater with Seebri Breezhaler than with the long-acting muscarinic antagonist tiotropium, the treatment difference ranged from 0.030 L to 0.068 L. The bronchodilator effect of Seebri Breezhaler was sustained over 24 hours. There was no evidence for tachyphylaxis to the bronchodilator effect after repeated dosing for up to 52 weeks.

Secondary Pharmacodynamic Effects

The effect on heart rate and QTc interval of glycopyrronium bromide 150 µg (equivalent to 120 µg glycopyrronium) administered intravenously was investigated in young healthy subjects. Peak exposures (C_{max}) about 50-fold higher than after inhalation of Seebri Breezhaler 50 µg at steady state were achieved and did not result in tachycardia or QT(c) prolongation. Negligible signs of bradycardia were observed (mean difference over 24 h -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 µg in COPD patients.

Pharmacokinetics (PK)

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 was estimated to be about 5%.

Following repeated once-daily inhalation in patients with COPD, 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 µg once-daily dosing regimen were 166 pg/mL and 8 pg/mL, respectively. With once-daily doses of 100 and 200 µg, 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 µg.

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 µg once-daily dosing regimen.

Biotransformation/metabolism

In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide 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 bromide 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 bromide has no relevant capacity

to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. *In vitro* enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide 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 [^{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 µg 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 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.

Linearity/non-linearity

In COPD patients' systemic exposure as well as total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the dose range of 50 µg to 200 µg.

Special populations

A population PK analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Seebri Breezhaler 50 µg once-daily can be safely used in all age and body weight groups.

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

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 section Clinical Pharmacology – Elimination). Impairment of the hepatic metabolism of glycopyrronium is not thought 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 bromide. A moderate mean increase in total systemic exposure (AUClast) 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. Using a population PK analysis, it was concluded that in COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate eGFR≥30 mL/min/1.73m^2) Seebri Breezhaler can be used at the recommended dose.

Ethnicity

There were no major differences in total systemic exposure (AUC) between Japanese and Caucasian subjects following inhalation of glycopyrronium bromide. Insufficient PK data is available for other ethnicities or races.

CLINICAL STUDIES

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) which 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%. Efficacy and safety of Seebri Breezhaler beyond 1 year has not been evaluated.

Lung function

In these studies, Seebri Breezhaler, administered at 50 microgram once-daily showed clinically meaningful improvements in lung function (as measured by the forced expiratory volume in one second, FEV_1) over 24 hours. At the 12-week primary endpoint (24-hour trough FEV_1), Seebri Breezhaler provided bronchodilation benefits of 0.108 L and 0.097 L compared to placebo ($p<0.001$) for the 6- and 12-month study respectively. In the latter study, the improvement vs. placebo for the open-label tiotropium 18 microgram once-daily arm was 0.083 L ($p < 0.001$).

In both studies Seebri Breezhaler demonstrated a rapid onset of bronchodilator effect. 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. 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 12-month study, Seebri Breezhaler also produced statistically significant improvements in FEV_1 compared to tiotropium in the first 4 hours after dosing on day 1 by 0.056 L ($p < 0.001$) and at week 26 by 0.050 L ($p=0.005$), and numerically greater values for FEV_1 in the first 4 hours after dosing than tiotropium at week 12 (0.030 L) and week 52 (0.015 L).

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.

The improvements in mean trough FEV_1 observed at the primary endpoint (12 weeks) were maintained throughout treatment in both the 6- and 12-months studies. Mean trough FEV_1

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. These data indicate that the 24-hour bronchodilator effect of Seebri Breezhaler was maintained from the first dose throughout a one-year period.

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

Serial spirometry data was used to calculate FEV_1 standardized (for time) area under the curve (AUC). In the 6-month study for FEV_1 AUC 0-24h Seebri Breezhaler provided a benefit of 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 at Week 12, Seebri Breezhaler provided a benefit of 0.106 L for FEV_1 AUC 0-24h ($p<0.001$) compared to placebo; for tiotropium the treatment difference was 0.079 L compared to placebo ($p=0.014$). At Week 52 in the 12-month study Seebri Breezhaler provided a benefit of 0.106 L for FEV_1 AUC 0-24h compared to placebo ($p<0.001$); for tiotropium the treatment difference compared to placebo was 0.040 L ($p=0.279$).

The magnitude of the bronchodilator effect with Seebri Breezhaler was dependent on the degree of reversibility of airflow limitation at baseline (tested by administration of a short-acting muscarinic antagonist bronchodilator): Patients with the lowest degree of reversibility at baseline (<5%) generally exhibited a lower bronchodilator response than patients with a higher degree of reversibility at baseline (≥5%). At 12 weeks (primary endpoint), Seebri Breezhaler increased trough FEV_1 by 0.072 L in patients with the lowest degree of reversibility (<5%) and by 0.113 L in those patients with a higher degree of reversibility at baseline (≥5%) compared to placebo (both $p<0.05$). Similar findings were observed with patients receiving tiotropium. Following 12 weeks treatment with tiotropium, patients with the lowest degree of reversibility at baseline (<5%) were found to have an increase in trough FEV_1 of 0.059 L compared to placebo, while those patients with a higher degree of reversibility at baseline (≥5%) were found to have an increase in trough FEV_1 of 0.097 L compared to placebo.

Figure 1 Six-month pivotal study: Serial spirometry data (least square means of FEV_1 (L)) after first dose

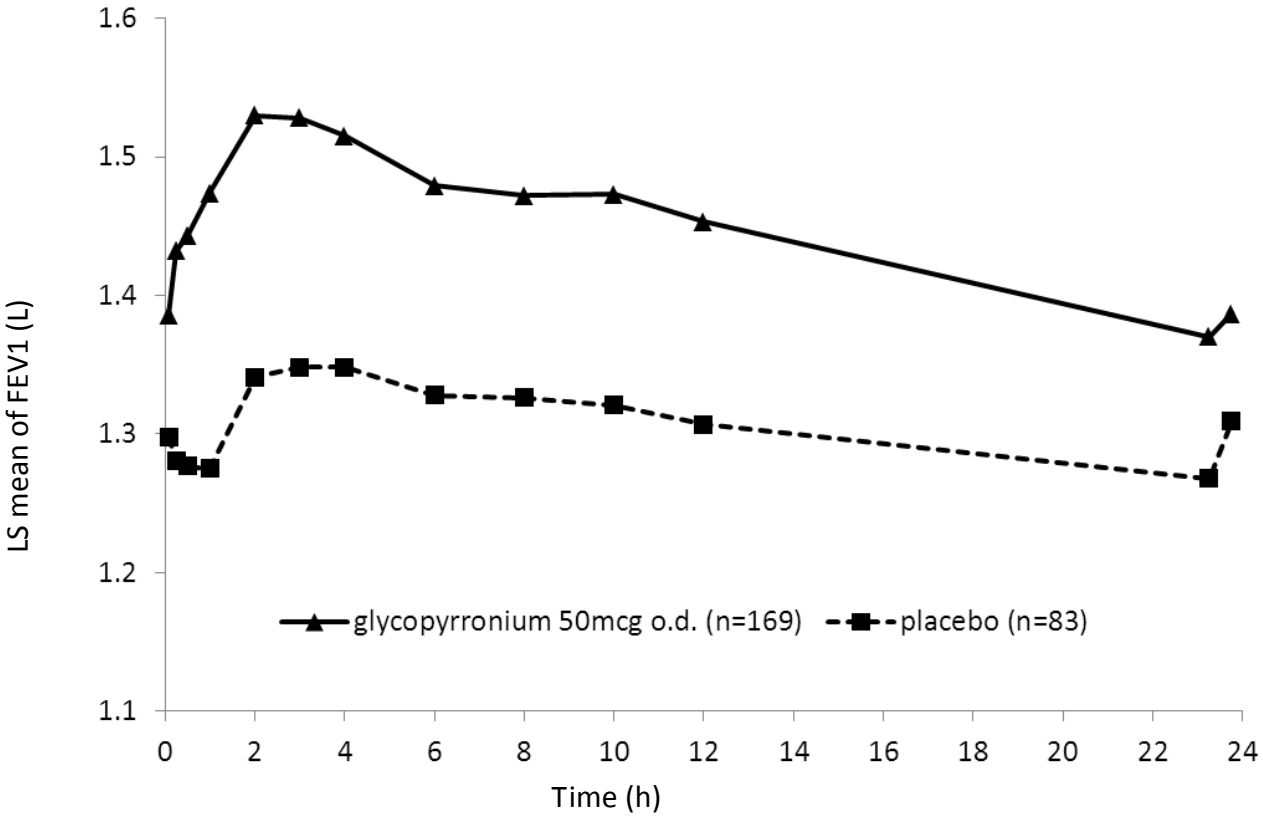


Figure 2 **Six-month pivotal study: Serial spirometry data (least square means of FEV_1 (L)) at week 12**

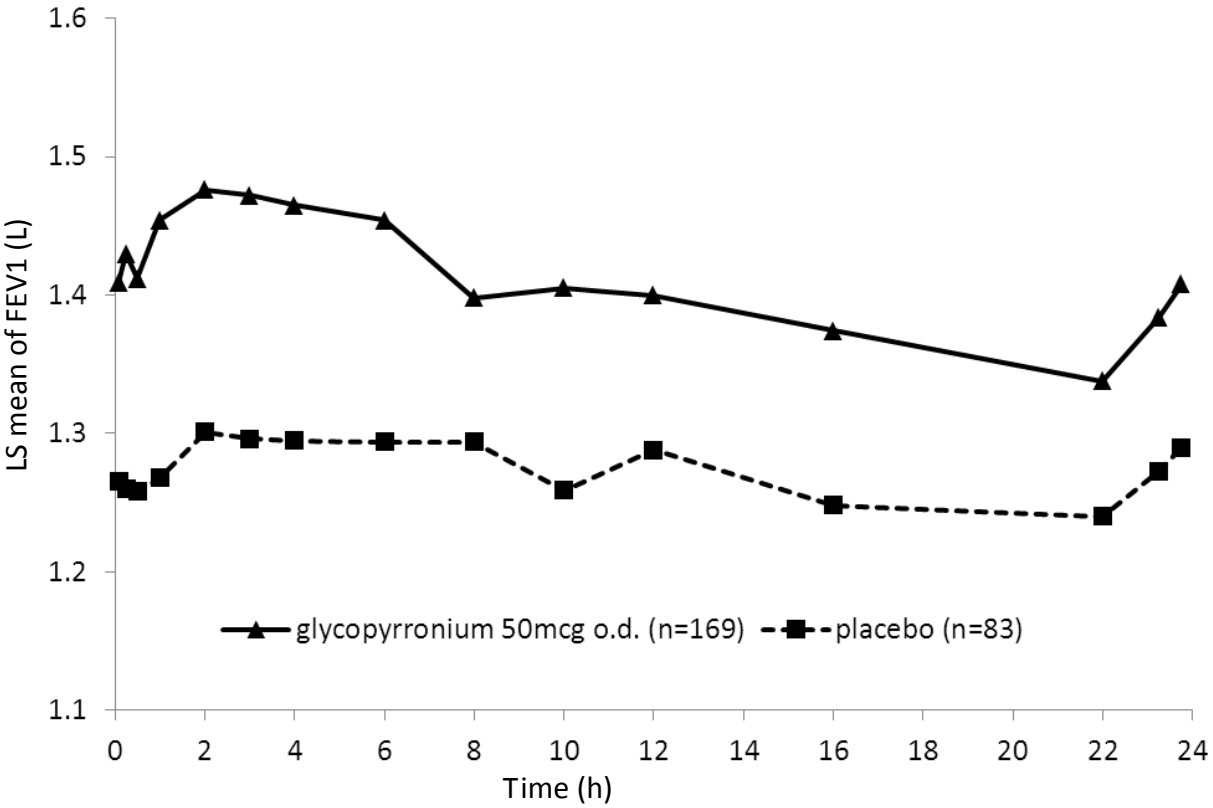


Figure 3 **Twelve-month pivotal study: Serial spirometry data (least square means of FEV_1 (L)) after first dose**

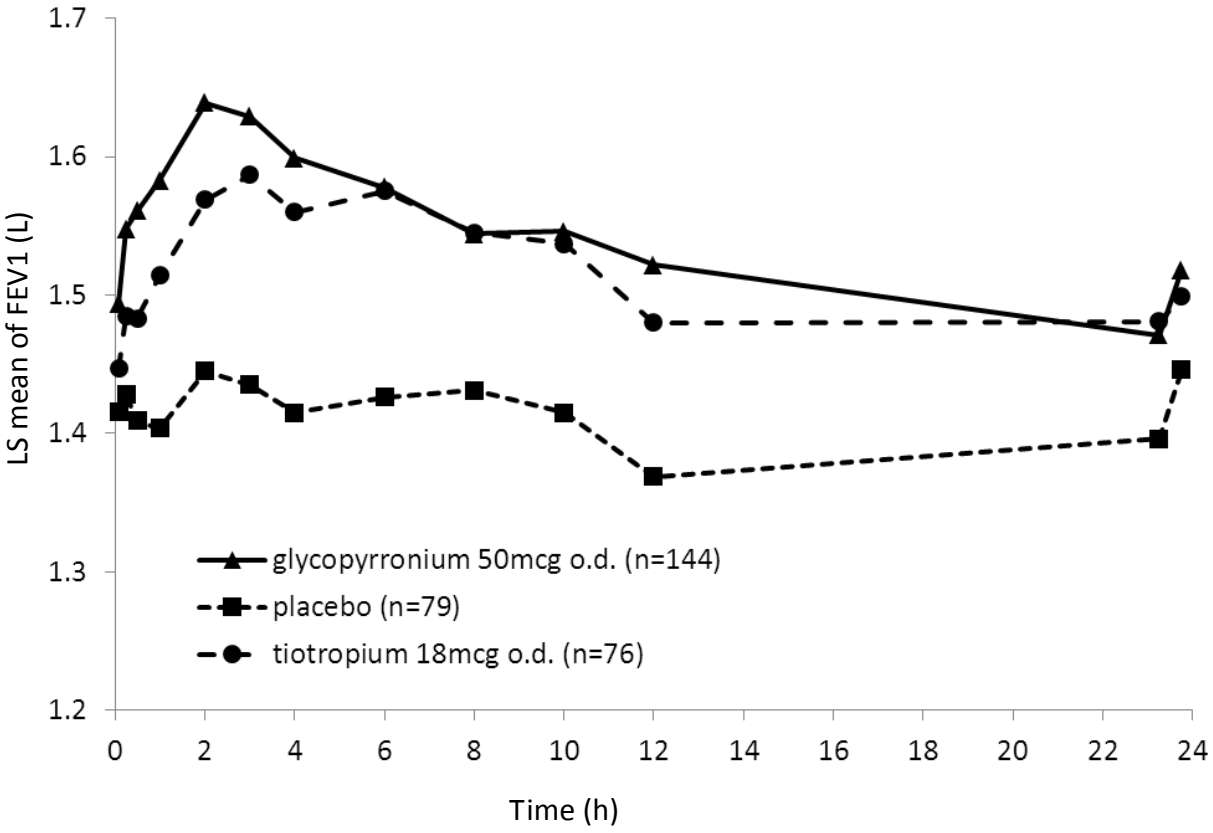
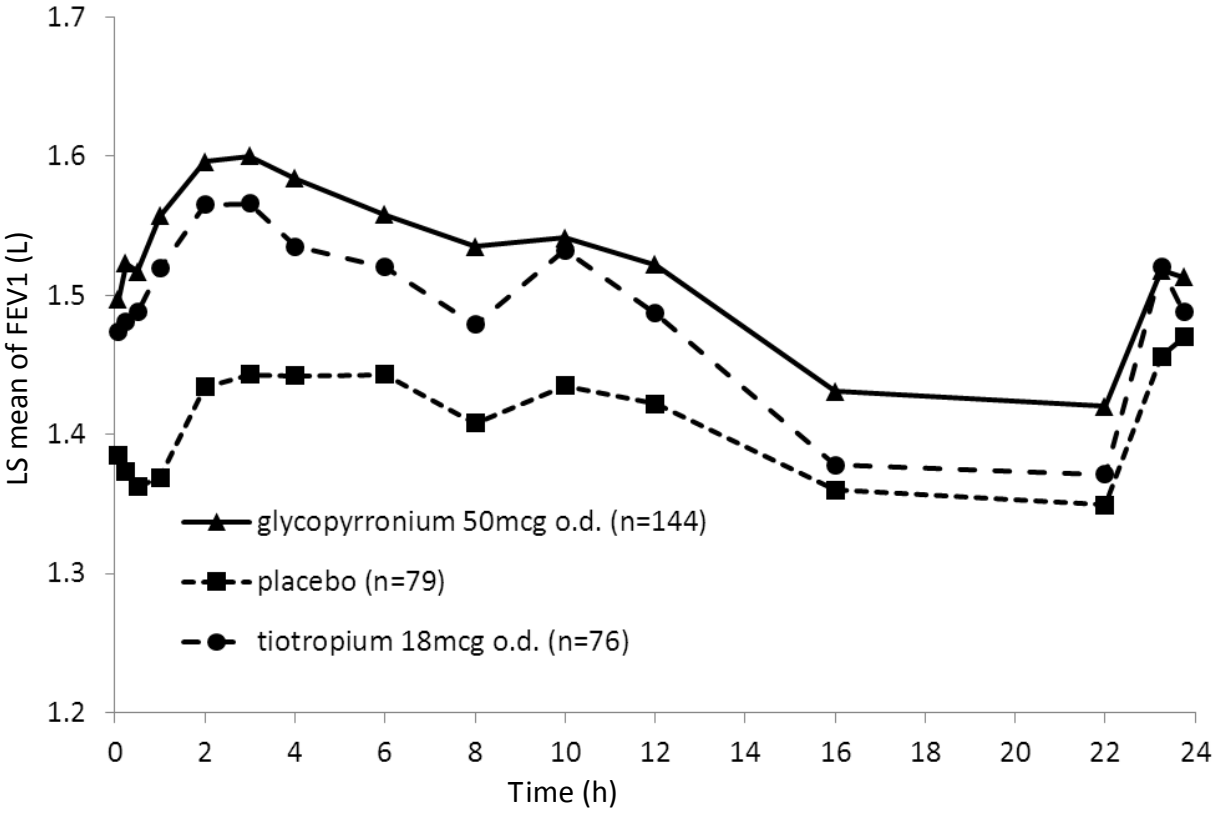


Figure 4 Twelve-month pivotal study: Serial spirometry data (least square means of FEV_1 (L)) at week 12



In addition to demonstrating improvements in FEV_1, Seebri Breezhaler consistently improved forced vital capacity (FVC) and inspiratory capacity (IC) in the two pivotal studies. At Week 12 Seebri Breezhaler was shown to increase mean trough FVC by 0.194 L and 0.183 L compared to placebo ($p<0.001$) in the 6- and 12-month studies respectively. Seebri Breezhaler improved trough IC 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.

Symptomatic benefit

Seebri Breezhaler administered at 50 µg once-daily significantly reduced breathlessness as evaluated by the Transitional Dyspnea Index (TDI). In a pooled analysis of the 6- and 12-month pivotal studies the percentage of patients responding with a clinically meaningful difference of ≥ 1 point improvement in the TDI focal score at Week 26 was 58.4% for Seebri Breezhaler compared with 46.4% for patients receiving placebo and 53.4% for patients receiving tiotropium. The differences in responder rates were statistically significant for the comparison of Seebri Breezhaler to placebo (<0.001) and tiotropium to placebo (p=0.009).

Seebri Breezhaler 50 µg once-daily has also a significant effect on health status measured using the St. George's Respiratory Questionnaire (SGRQ). A pooled analysis of the 6- and 12-month pivotal studies found the percentage of patients responding with a clinically important improvement in the SGRQ total score (≤ -4) at Week 26 was 57.8% for Seebri Breezhaler compared with 47.6% for patients receiving placebo and 61.0% for patients receiving tiotropium. The differences in responder rates were statistically significant for the comparison

of Seebri Breezhaler to placebo (<0.001) and tiotropium to placebo (p=0.004).

In a pooled analysis of the 6- and 12-month studies, Seebri Breezhaler 50µg once-daily significantly prolonged the time to first moderate or severe COPD exacerbation and reduced the rate of moderate or severe COPD exacerbations (moderate exacerbations were those requiring treatment with systemic corticosteroids and/or antibiotics, severe exacerbations those resulting in hospitalization). The proportion of patients with moderate or severe COPD exacerbations in the 26-week pooled analysis was 19.8% for Seebri Breezhaler vs. 27.2% for placebo and the estimated risk ratio for time to moderate or severe exacerbations was 0.64 [95% CI: 0.520, 0.799; p < 0.001], suggesting a 36% risk reduction vs. placebo, similarly the estimated risk ratio for time to first severe exacerbation leading to hospitalization was 0.39 [95% CI: 0.205, 0.728; p = 0.003]. Over the 26-week pooled analysis the exacerbation rate was statistically significantly lower for patients treated with Seebri Breezhaler compared to those treated with placebo, the rate ratio being 0.66 ([95% CI: 0.525, 0.841; p < 0.001]).

Seebri Breezhaler 50µg once-daily significantly reduced the use of rescue medication by 0.46 puffs per day (p = 0.005) over 26 weeks and by 0.37 puffs per day (p = 0.039) over 52 weeks compared to placebo for the 6- and 12-month studies, respectively.

The effect of Seebri Breezhaler reducing dynamic hyperinflation and the associated improvements in exercise tolerance were investigated in a randomized, double-blind, placebo-controlled trial in 108 patients with moderate to severe COPD. Seebri Breezhaler achieved its full effect of improving inspiratory capacity under exercise (0.23 L) and has statistically significant effects on exercise endurance of 43 seconds (an increase of 10%) after the first dose. After three weeks of treatment Seebri Breezhaler improved exercise endurance time by 89 seconds (an increase of 21%) and inspiratory capacity under exercise was increased by 0.20 L. Seebri Breezhaler was found to decrease dyspnea and leg discomfort when exercising as measured using Borg scales. Seebri Breezhaler also reduced dyspnea at rest measured using the Transitional Dyspnea Index.

NON-CLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

The effects seen during repeated-dose inhalation toxicity studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium bromide or mild local irritation. These included mild to moderate increases in heart rate 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 with limited relevance for therapeutic use in patients. 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 and therefore indicate limited relevance during clinical use.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide. 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 μg once-daily for humans.

Published data for glycopyrronium bromide do not indicate any reproductive toxicity issues. Seebri Breezhaler was not teratogenic in rats or rabbits following inhalation administration. Reproduction studies in rats and other data in animals did not indicate a concern regarding fertility in either males or females or pre- and post-natal development.

Glycopyrronium bromide and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Glycopyrronium bromide (including its metabolites) was excreted into the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam.

STORAGE

See folding box.

Seebri Breezhaler should not be used after the date marked "EXP" on the pack.

Seebri Breezhaler must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

For correct administration/use of the product please refer to section DOSAGE AND ADMINISTRATION.

INFORMATION FOR PATIENTS

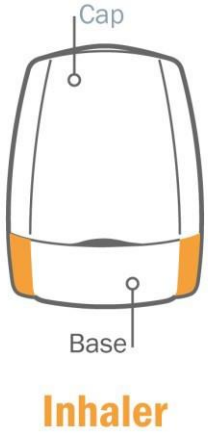
This part of the leaflet explains how to use and care for your Seebri Breezhaler inhaler. Please read carefully and follow these instructions.

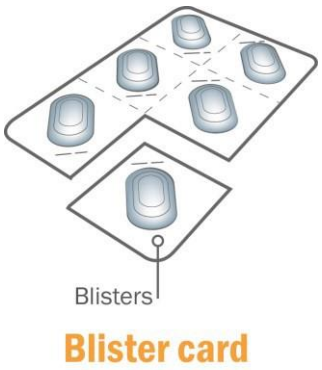
If you have any questions, **ask your doctor or pharmacist**.

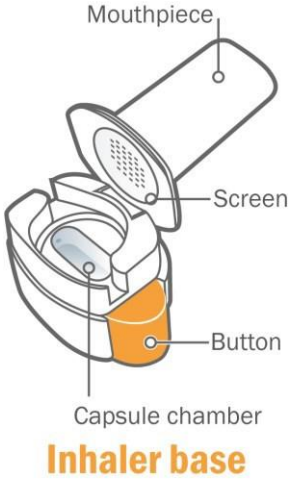
Your Seebri Breezhaler pack

One Seebri Breezhaler pack contains:

- One Seebri Breezhaler inhaler
- One or more blisters containing Seebri Breezhaler capsules to be used in the inhaler







Only use the Seebri Breezhaler inhaler contained in this pack. Do not use Seebri Breezhaler capsules with any other inhaler, do not use Seebri Breezhaler inhaler to take any other capsule medicine.

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

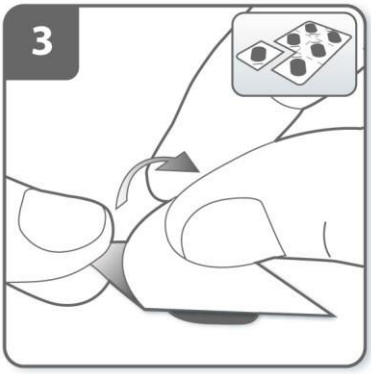
Do not swallow Seebri Breezhaler capsules. The powder in the capsules is for you to inhale.

How to use your 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 a 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 capsule.

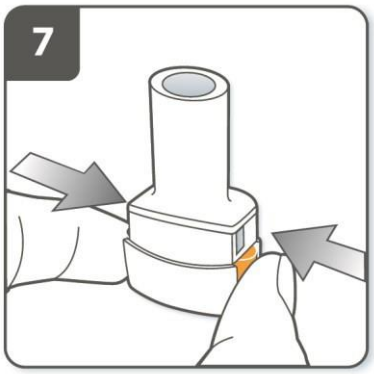
Insert capsule:

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.

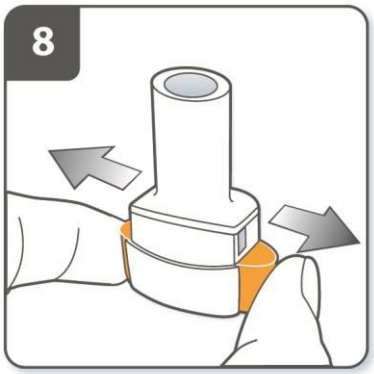


Pierce the capsule:

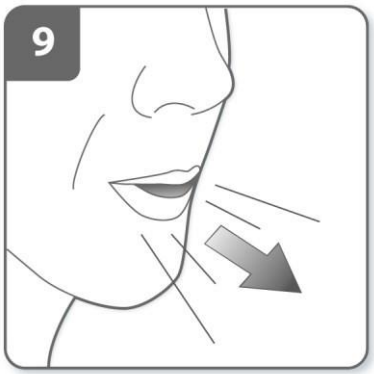
Hold the inhaler upright with the mouthpiece pointing up.

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:

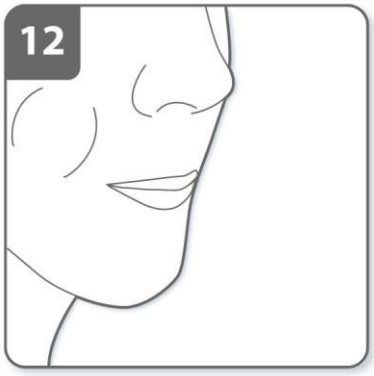
Before breathing in:

- 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 flavor 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.

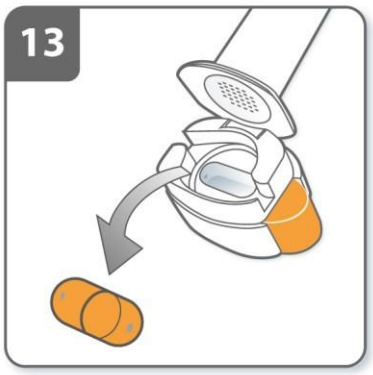


Hold breath:

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 a 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 use the new Seebri Breezhaler inhaler that comes with your new Seebri Breezhaler medication pack.
- Do not store the capsules in the Seebri Breezhaler inhaler.
- Always keep the Seebri Breezhaler inhaler and Seebri Breezhaler capsules in a dry place.

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.

Manufacturer:

See folding box.

Pack size:

Single pack of 6 capsules (1x6's) or 30 capsules (5 x 6's, 3 x 10's). Not all presentations may be available locally.

Country Specific Package Leaflet

Information issued: May 2016.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland