NOVARTIS

seebri™
breezhaler®

50 microgram/µg

Seebri® Breezhaler®
Hard capsules containing inhalation powder

سيبري® بريزهيلار®
كبسولات صلبة تحتوي على مسحوق للاستنشاق

2195698 R02

Composition

Active substance

Glycopyrronium as glycopyrronium bromide.

Excipients

Capsule fill: Lactose monohydrate, magnesium stearate.

Capsule shell components: Hypromellose, purified water, carrageenan, potassium chloride,

FDC Yellow 6 (110 Sunset Yellow FCF).

Information might differ in some countries

Pharmaceutical form and quantity of active substance per unit

50 µg, hard capsules containing inhalation powder.

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.

Quantity of active substance
Hard capsules containing 63 µg glycopyrronium bromide (equivalent to 50 µg glycopyrronium)
The dose administered (i.e. the dose discharged through the mouthpiece of the Seebri Breezhaler inhaler) is 44 µg glycopyrronium.

Indications/Potential uses

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

Dosage/Administration

General patient populations

Dosage

The recommended dosage of Seebri Breezhaler is the once-daily inhalation of the content of one 50 µg capsule using the Seebri Breezhaler inhaler. This daily dose should not be exceeded.

Special populations

Renal impairment

Seebri Breezhaler can be used at the recommended dose in patients with mild to moderate renal dysfunction. In patients with severe renal dysfunction or end-stage renal disease requiring dialysis, Seebri Breezhaler should be used only if the expected benefit outweighs the potential risk (see also “Warnings and precautions” and “Pharmacokinetics”).

Hepatic impairment
No specific studies have been conducted in patients with hepatic dysfunction. Seebri Breezhaler is predominantly cleared by renal excretion.

Elderly patients
Seebri Breezhaler can be used at the recommended dose in elderly patients 75 years of age and older.

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

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 also “Overdose”).

It is recommended to administer Seebri Breezhaler once daily at the same time 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 a day. Seebri Breezhaler capsules must always be stored in the blister pack to protect them from moisture and should only be removed IMMEDIATELY BEFORE USE.

When Seebri Breezhaler is prescribed, 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.

Contraindications

Hypersensitivity to the active substance, to lactose or to any of the other excipients.

Warnings and precautions

Not for acute use.

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

Hypersensitivity

Immediate hypersensitivity reactions have been reported after administration of Seebri Breezhaler. If signs of an allergic reaction occur, particularly angioo-edema (including difficulties breathing or swallowing, swelling of the tongue,

the lips and of the face) urticaria or skin rash, treatment with Seebri Breezhaler should be stopped immediately and an alternative treatment found.

Anticholinergic effect

Like other anticholinergic agents, Seebri Breezhaler should be used with caution in patients with narrow-angle glaucoma, urinary retention or severe pre-existing cardiovascular disease.

Patients should be advised to ensure that they do not get the powder in their eyes due to improper use and about signs and symptoms of acute narrow-angle glaucoma. They 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 dysfunction

For patients with severe renal dysfunction (estimated glomerular filtration rate below 30 ml/min/1.73 m^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 “Pharmacokinetics”). These patients should be monitored closely for potential adverse drug reactions.

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.

Excipients

Seebri Breezhaler contains the azo dye Sunset Yellow FCF (E 110). Caution is indicated when using Seebri Breezhaler in patients hypersensitive to azo dyes, acetylsalicylic acid or other prostaglandin inhibitors.

Seebri Breezhaler contains lactose and should therefore not be used in patients with severe lactase deficiency or galactosaemia.

Interactions

Pharmacodynamic interactions

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

Seebri Breezhaler has been used concomitantly with other medicines

commonly used in the treatment of COPD. There was no clinical evidence of drug interactions, even if no formal interaction studies were carried out. The concomitant medicines include sympathomimetic bronchodilators, methylxanthines as well as oral and inhaled steroids.

In healthy adults, co-administration of Seebri Breezhaler and orally inhaled indacaterol, a beta2-adrenergic agonist, under steady-state conditions of both active substances, did not affect the pharmacokinetics of either active substance.

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport that is thought to contribute to the renal excretion of glycopyrronium, increased total exposure (AUC) to glycopyrronium by 22% and decreased renal clearance by 23%.

In vitro studies indicate that Seebri Breezhaler is not likely to inhibit or induce

the metabolism of other medicines, nor processes involving drug transporters. Metabolic processes in which multiple enzymes are involved play a secondary role in the elimination of glycopyrronium (see "Pharmacokinetics"). Inhibition or induction of the metabolism of glycopyrronium is not likely to result in a relevant change of systemic exposure to the drug.

Pregnancy/Breast-feeding

Women of child-bearing potential

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

Pregnancy

No clinical data are available for pregnant COPD patients. Seebri Breezhaler was not teratogenic in rats or rabbits following inhalation (see "Preclinical data"). As there is insufficient experience in pregnant women, Seebri

Breezhaler should only be used during pregnancy after careful assessment of the benefits and risks.

Breast-feeding

It is not known whether glycopyrronium bromide passes into human breast milk. Seebri Breezhaler should only be used by breast-feeding women after careful assessment of the benefits and risks.

Effects on the ability to drive and to use machines

There have been no studies of the effects of Seebri Breezhaler on the ability to drive or to use machines.

Adverse effects

The safety and tolerability of Seebri Breezhaler has been explored at the recommended dose of 50 µg once daily in 1,353 COPD patients. Of these,

842 patients were treated for at least 26 weeks and 351 patients for at least 52 weeks. Patients with narrow-angle glaucoma, symptomatic prostatic hyperplasia, bladder neck stenosis, moderate renal impairment and relevant cardiovascular diseases (such as recent myocardial infarction, arrhythmias, left ventricular failure) were not investigated in the large clinical efficacy and safety studies.

The safety profile is characterised by symptoms related to the anticholinergic effect, including dry mouth, while other gastrointestinal effects and signs of urinary retention were infrequent. Adverse effects related to local tolerability included throat irritation, nasopharyngitis, rhinitis and sinusitis. At the recommended dose, Seebri Breezhaler is devoid of effects on blood pressure or heart rate.

Adverse effects reported during the first 6 months of two pooled pivotal Phase III studies of 6 and 12 months' duration are listed by MedDRA system organ class. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections
Uncommon: Rhinitis, cystitis.

Metabolism and nutrition disorders
Uncommon: Hyperglycaemia.

Psychiatric disorders
Uncommon: Insomnia.

Nervous system disorders
Uncommon: Hypoaesthesia.

Cardiac disorders
Uncommon: Atrial fibrillation, palpitations.

Respiratory disorders
Uncommon: Sinus congestion, productive cough, throat irritation, epistaxis.

Gastrointestinal disorders
Common: Dry mouth, gastroenteritis.
Uncommon: Dyspepsia, dental caries.

Skin and subcutaneous tissue disorders
Uncommon: Rash.

Musculoskeletal disorders
Uncommon: Pain in the extremities, musculoskeletal chest pain.

Renal and urinary disorders
Uncommon: Dysuria, obstructive uropathy.

General disorders
Uncommon: Fatigue, asthenia.
In the 12-month study, the following additional events 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 effects based on spontaneous reports and literature cases (frequency unknown)

The following adverse effect was reported in post-marketing experience with Seebri Breezhaler: Angiooedema, hypersensitivity, paradoxical bronchospasms, dysphonia, pruritus (unknown frequency).

Description of selected adverse effects

The most common anticholinergic adverse effect was dry mouth. The majority of the reports of dry mouth were suspected to be related to the medicine and were of a mild degree, none were severe. A higher number of neoplasias were observed with glycopyrronium than with placebo. The reason for this imbalance is not known.

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.

Overdose

High dosages of glycopyrronium may lead to anticholinergic signs and symptoms for which symptomatic treatment may be indicated.
In COPD patients, repeat orally inhaled administration of Seebri Breezhaler at total doses of 100 and 200 µg once daily for 28 days was well tolerated.
Acute intoxication by inadvertent oral ingestion of Seebri Breezhaler capsules is unlikely due to the low 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. These doses were well tolerated.

Properties/Actions

ATC code: R03BB06

Mechanism of action

Seebri Breezhaler is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) for inhaled 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 greater selectivity for the human M3 and M1 receptors than for the human M2 receptor in competitive binding studies. It has a rapid onset of action, as evidenced by observed kinetic parameters for receptor association/dissociation and the onset of action after inhalation in clinical studies.
Owing to the prolonged terminal elimination half-life of glycopyrronium after inhalation using the Seebri Breezhaler inhaler, in contrast to the half-life after i.v. administration, the long duration of action is presumably partly due to the sustained active substance concentration in the lungs (see “Pharmacokinetics“).

Pharmacodynamics

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 of inhalation of Seebri Breezhaler, with an increase in FEV_1 relative to baseline ranging from 0.091 litres to 0.094 litres. In the 52-week study, Seebri Breezhaler produced a significantly higher value for FEV_1 compared to tiotropium on Day 1 and at Week 26. FEV_1 was also numerically higher in the first 4 hours after administration of Seebri Breezhaler compared to tiotropium at Week 12 and Week 52.

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

No change in mean heart rate or QTc interval was observed with Seebri Breezhaler at doses up to 176 µg in COPD patients. In a thorough QT study in 73 healthy volunteers, a single inhaled dose of 352 µg glycopyrronium (8 times the therapeutic dose) did not prolong the QTc interval and slightly reduced the heart rate (maximum effect: -5.9 bpm; average effect over 24 hours: -2.8 bpm) when compared to placebo. The effect on heart rate and QTc interval of 150 µg glycopyrronium bromide (equivalent to 120 µg glycopyrronium) administered intravenously was investigated in young healthy subjects. The peak concentrations (C_{max}) achieved were about 50 times higher

than exposure following inhalation of 44 µg glycopyrronium at steady state and did not result in tachycardia or QTc prolongation. A slight reduction in heart rate (mean difference over 24 hours: -2 bpm when compared to placebo), which is a known effect of low exposures to anticholinergic concentrations in young healthy subjects, was observed.-
In a thorough QT/QTc study in 73 healthy volunteers, a single inhaled dose of 352 µg Seebri Breezhaler (8 times the therapeutic dose) did not prolong the QTc interval but slightly reduced the heart rate (maximum effect 5.9 bpm; average effect over 24 hours 2.8 bpm) when compared to placebo.

Clinical efficacy

The Seebri Breezhaler Phase III clinical development programme consisted of two pivotal studies (a 6-month placebo-controlled study and a 12-month

placebo- and active-controlled study), which enrolled a total of 1,888 patients with a clinical diagnosis of COPD. The patients 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%. Patients with cardiac disease and/or contraindications to anticholinergics were excluded.

Lung function

In these studies, Seebri Breezhaler, administered at 50 µg 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 an improvement in bronchodilation of 0.108 litres and 0.097 litres compared to

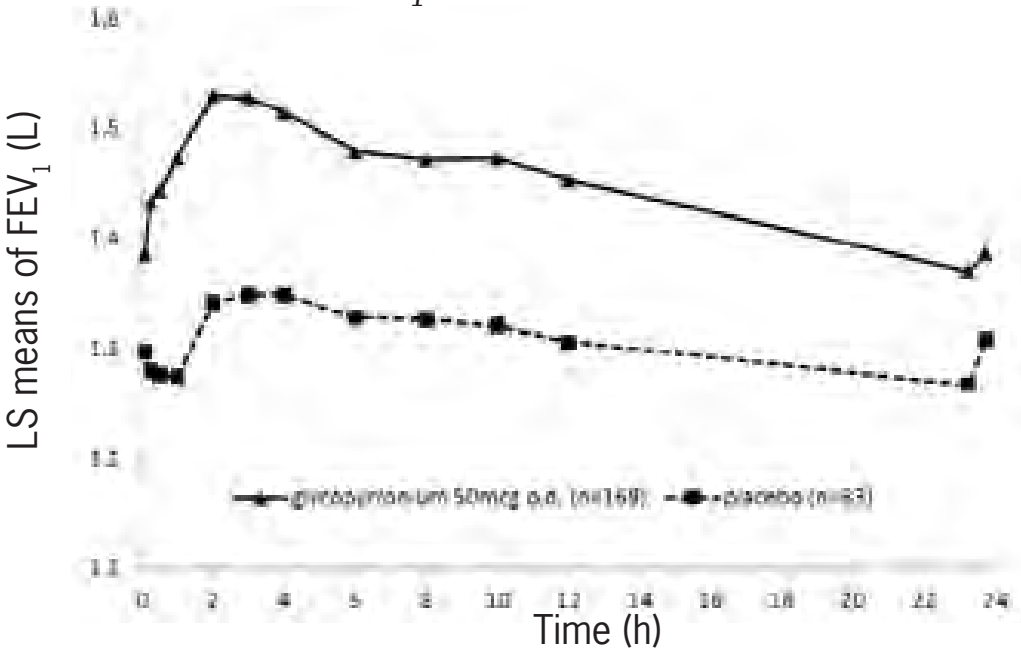
placebo (p<0.001) for the 6 and 12-month study, respectively. In the second study, the improvement vs. placebo for the open-label tiotropium 18 µg once-daily arm was 0.083 litres (p < 0.001).
In the pivotal studies, there was a rapid onset of action within 5 minutes of inhalation of Seebri Breezhaler, with an increase in FEV_1 relative to baseline ranging from 0.091 litres to 0.094 litres.
The improvements in mean trough FEV_1 observed at the primary endpoint (12 weeks) were maintained throughout the entire duration of treatment in both the 6 and 12-month studies. Compared to placebo, mean trough FEV_1 increased by 0.1008 litres at Week 12 and by 0.113 litres at Week 26 of the 6-month study. In the 12-month study, it was increased by 0.097 litres at Week 12 and by 0.108 litres at Week 52.
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 1-1), at Week 12 (Fig 1-2) and at Week 26. In the 12-month study, serial spirometry was performed on Day 1 (Fig 1-3), at Week 12 (Fig 1-4) and at Week 52.
Serial spirometry data were used to calculate FEV_1 standardised (for time) area under the curve (AUC). At Week 12 and Week 26 of the 6-month study, Seebri Breezhaler improved FEV_1 AUC 0-24h by 0.133 litres and 0.199 litres, respectively, compared to placebo ($p<0.001$). At Week 12 of the 12-month study, Seebri Breezhaler improved FEV_1 AUC 0-24h ($p<0.001$) by 0.106 litres compared to placebo; for tiotropium, the treatment difference was 0.079 litres compared to placebo ($p=0.014$). At Week 52 of the 12-month study, Seebri Breezhaler improved FEV_1 AUC 0-24h ($p<0.001$) by 0.106 litres

compared to placebo; for tiotropium, the treatment difference was 0.040 litres compared to placebo (p=0.279).
The strength of the bronchodilator effect of Seebri Breezhaler is possibly dependent on the degree of reversibility of airflow limitation at baseline (tested by administration of a short-acting muscarinic antagonist bronchodilator). In corresponding secondary subgroup analyses, 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 litres in patients with the lowest degree of reversibility at baseline (<5%) and by 0.113 litres in those patients with a higher degree of reversibility at baseline (≥5%) compared to placebo (both p<0.05). Similar findings were observed in patients receiving tiotropium. Following 12 weeks of

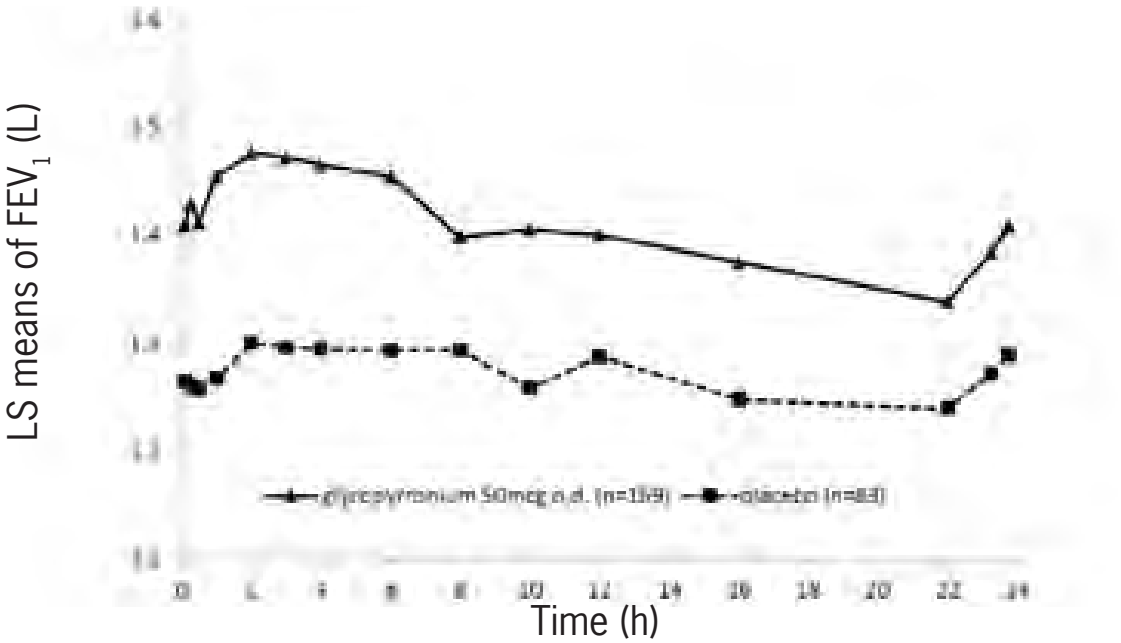
treatment with tiotropium, patients with the lowest degree of reversibility at baseline (<5%) were found to have an increase in trough FEV_1 of 0.059 litres compared to placebo, while those patients with a higher degree of reversibility at baseline (≥5%) were found to have an increase in trough FEV_1 of 0.097 litres compared to placebo.

Figure 1-1 6-month pivotal study: Serial spirometry data (least square means of FEV_1 (l)) after first dose



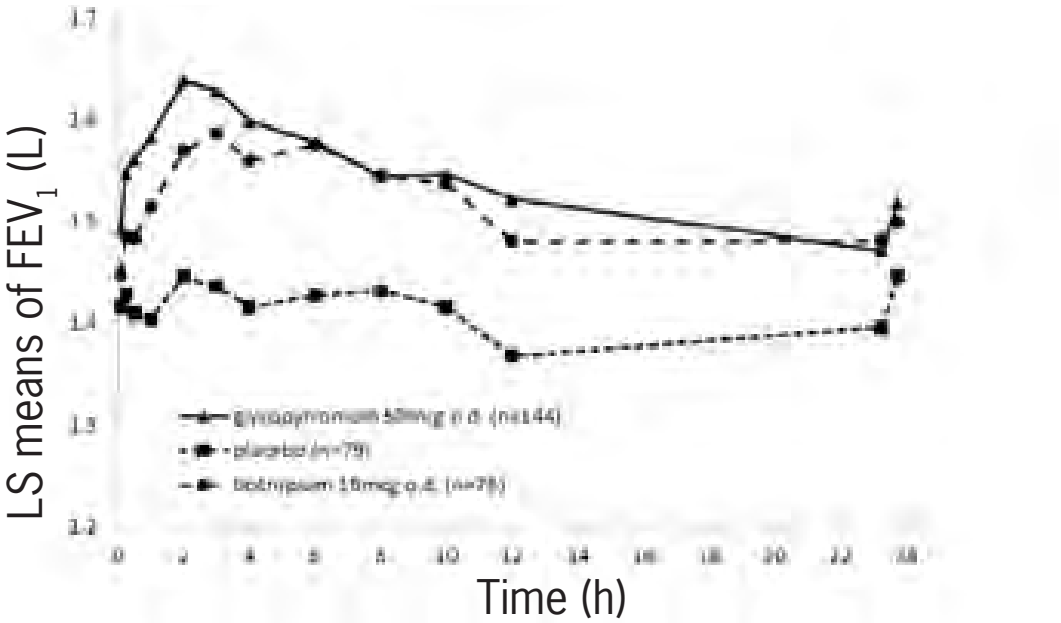
(Key:) Glycopyrronium 50 µg once daily (n=169), placebo (n=83)

Figure 1-2 6-month pivotal study: Serial spirometry data (least square means of FEV_1 (l)) at Week 12



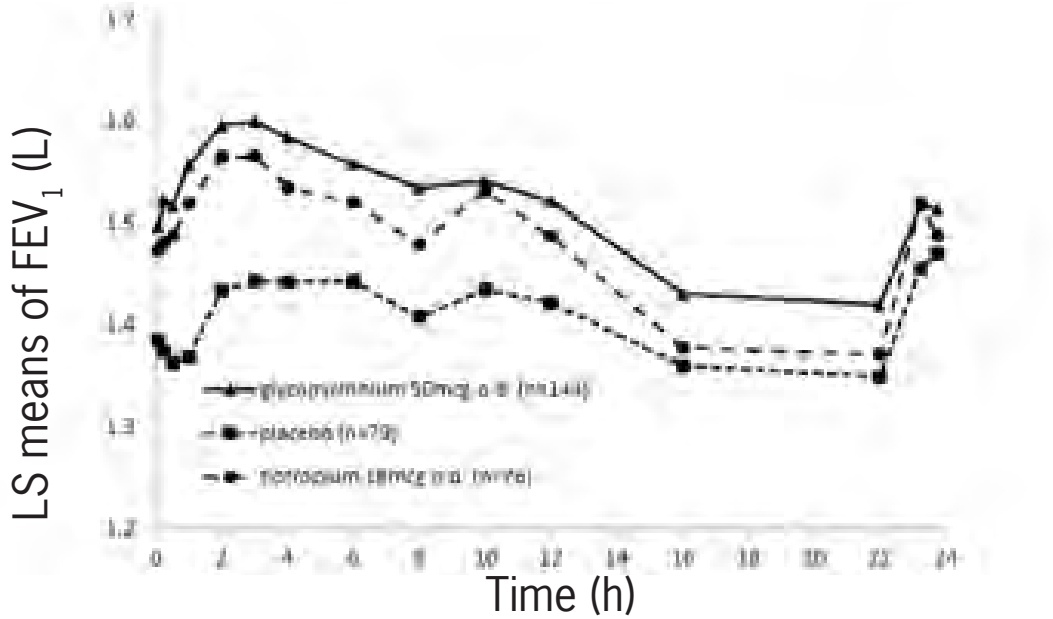
(Key:) 50 µg glycopyrronium once daily (n=169), placebo (n=83)

Figure 1-3 12-month pivotal study: Serial spirometry data (least square means of FEV_1 (l)) after first dose



(Key:) 50 µg glycopyrronium once daily. (n=144), placebo (n=79), 18 µg tiotropium once daily (n=76)

Figure 1-4 12-month pivotal study: Serial spirometry data (least square means of FEV_1 (l)) at Week 12



(Key:) 50 µg glycopyrronium once daily (n=144), placebo (n=79), 18 µg tiotropium once daily (n=76)

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 litres and 0.183 litres 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 litres and 0.129 litres compared to placebo ($p<0.001$) in the 6 and 12-month studies, respectively.

Symptomatic benefit

Seebri Breezhaler 50 µg once daily significantly reduced dyspnoea as evaluated by the Transitional Dyspnoea Index (TDI). In a pooled analysis of the 6 and 12-month pivotal studies, the percentage of patients responding with a clinically meaningful improvement of ≥ 1 point in the TDI focal score at Week

26 was 58.4% for Seebri Breezhaler compared to 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 that the percentage of patients responding with a clinically meaningful improvement in the SGRQ total score (≤ -4) at Week 26 was 57.8% for Seebri Breezhaler, compared to 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 50 µg 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 were those resulting in hospitalisation.) 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 hospitalisation was 0.39 [95% CI: 0.205, 0.728; p = 0.003]. In 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]).
Compared to placebo, Seebri Breezhaler 50 µg 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 for the 6 and 12-month studies, respectively.
The effect of Seebri Breezhaler in reducing dynamic hyperinflation and the associated improvements in exercise tolerance, were investigated in a randomised, double-blind, placebo-controlled study in 108 patients with moderate to severe COPD. Seebri Breezhaler achieved its full effect of improving inspiratory capacity during exercise (0.23 litres) and has a statistically significant effect 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 litres.
Borg scale measurements showed that Seebri Breezhaler reduces dyspnoea and leg discomfort. The reduction in dyspnoea at rest was also measured using the Transitional Dyspnoea Index (TDI).

Pharmacokinetics

Absorption

Following oral inhalation using the Seebri Breezhaler inhaler, glycopyrronium was rapidly absorbed and reached peak plasma concentrations 5 minutes post-dose.
The absolute bioavailability of glycopyrronium inhaled using the 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 5%.

Following repeated once-daily inhalation in patients with COPD, pharmacokinetic steady state of glycopyrronium was reached within one week of treatment. The 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.

Distribution

After i.v. administration, the steady-state volume of distribution (Vss) of glycopyrronium was 83 litres and the volume of distribution in the terminal phase (Vz) was 376 litres. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7,310 litres, which reflects much slower elimination after inhalation. *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 times higher than the steady-state mean peak levels achieved in plasma with a 50 µg once-daily dosing regimen.

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. Hydrolysis to M9 is likely to be catalysed by members of the cholinesterase family.
Following inhalation, systemic exposure to M9 was on average in the same order of magnitude as 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 by pre-systemic hydrolysis of the swallowed dose fraction of orally inhaled glycopyrronium bromide and/or via first-pass metabolism. Following inhalation or i.v. administration, only minimal amounts of M9 were

found in the urine (≤ 0.5% of the dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in human urine after repeated inhalation, accounting for about 3% of the dose.

In vitro inhibition studies suggest 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 clinically relevant induction of any of the cytochrome P450 isoenzymes tested, of UGT1A1 or of the transporters MDR1 and MRP2 by glycopyrronium bromide.

Elimination

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

Renal elimination of the parent drug accounts for about 60 to 70% of total clearance of systemically available glycopyrronium and non-renal clearance processes account for about 30 to 40%. Biliary clearance contributes to 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 to 24.4 litres/

hour. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20% of the dose was found in the urine as a 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 sustained lung absorption and/or transfer of glycopyrronium into systemic circulation at and beyond 24 hours after inhalation.

Linearity

In COPD patients, systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased approximately in proportion to the dose over the dose range of 50 to 200 µg.

Pharmacokinetics in special populations

A population pharmacokinetic analysis of data in COPD patients identified body weight and age as factors contributing to interpatient variability in systemic exposure. The data indicate that Seebri Breezhaler 50 µg once daily can also be used in older and elderly COPD patients, and in all body weight groups, without any increased risks.

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

Patients with renal impairment

Renal impairment has an impact on systemic exposure to glycopyrronium bromide. A mild to moderate increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal dysfunction.

An up to 2.2-fold increase was seen in subjects with severe renal dysfunction and end-stage renal disease. Using a population pharmacokinetic analysis, it was concluded that in COPD patients with mild and moderate renal dysfunction (estimated glomerular filtration rate eGFR ≥30 ml/min/1.73 m^2), Seebri Breezhaler can be used at the recommended dose.

Patients with hepatic impairment

No clinical studies have been conducted in patients with hepatic dysfunction. Glycopyrronium is predominantly cleared from the circulation by renal excretion (see “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Seebri Breezhaler have not been studied in children and adolescents below the age of 18. Seebri Breezhaler is not indicated for use in paediatric patients.

Elderly patients

The mechanism for elimination, and results from population pharmacokinetic studies, suggest that dose adjustment is not necessary in elderly patients.

Ethnicity

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

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential and reproductive and developmental toxicity.

The effects seen during repeat-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 rats and dogs associated with reduced secretions from the salivary, lacrimal and Harderian glands and pharynx. Lens opacities observed during chronic studies in rats have also 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 for clinical use.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide. Carcinogenicity studies in transgenic mice (oral administration) and rats (inhalation administration) revealed no evidence of carcinogenicity at systemic exposures (AUC) approximately 53 times higher in mice and 75 times higher in rats than following the maximum recommended dose of 50 µg once daily in 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. Reproductive studies in rats and other data in animals did not indicate problems 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.

Other information

Shelf life Do not use after the expiry date (= EXP) printed on the pack.Special precautions for storage

Keep out of the reach of children.

Store in the original pack and protect from moisture. Do not store above 30°C.

Instructions for use and handling

See “Dosage/Administration” for information on correct administration/use of the product. Detailed instructions for use are included in the patient information. Patients must use the new Seebri Breezhaler inhaler contained in each pack.

Pack sizes
Country specific pack sizes.

Manufacturer
See folding box.

Information last revised
November 2016

® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

INSTRUCTIONS FOR USE OF SEEBRI BREEZHALER INHALER

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

See also section **3. How to use SEEBRI BREEZHALER** of this leaflet. 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 capsule through foil.

Remove a SEEBRI capsule:
Capsules should always be stored in the blister and only removed immediately before use.

With dry hands, remove capsule from the blister.

Do not swallow SEEBRI 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.

8

Release the buttons fully.

9

Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully. **Never blow into the mouthpiece.**

10

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.**

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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 flavour 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.

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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.

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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.