NOVARTIS

SEEBRI BREEZHALER® (glycopyrronium bromide)

50 µg dry powder inhalation capsules

Professional Information

Document status: Final

Release date: 18 August 2020

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINAL PRODUCT

SEEBRI BREEZHALER® dry powder inhalation capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect

SEEBRI BREEZHALER contains Lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard hypromellose capsule: Transparent orange cap and body. Imprint - Cap: black " " under radial black bar; Body: black "GPL 50" above black radial bar. Size: 3.

Powder: White to practically white powder is contained in the capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SEEBRI BREEZHALER is indicated as a maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of 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.

Paediatrics

SEEBRI BREEZHALER should not be used in patients under 18-years of age, COPD is an indication of adults only.

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 4.9 Overdose*).

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 (*See Instructions for handling and use, section 6.6 Special precautions for disposal and other handling*).

4.3 Contraindications

- Hypersensitivity to glycopyrronium, lactose or any excipient listed under *Composition. (see section 4.4 Special warnings and precautions for use)*

Severe renal impairment CrCl < 30 ml/min.

4.4 Special warnings and precautions for use

Not for acute use

SEEBRI BREEZHALER is a once-daily 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

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

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.

Lactose

SEEBRI BREEZHALER contains lactose. Patients with rare hereditary problems of lactose intolerance or severe lactase deficiency should not use SEEBRI BREEZHALER.

4.5 Interaction with other medicines and other forms of interaction

The co-administration of SEEBRI BREEZHALER with inhaled anticholinergic-containing medicines has not been studied and is therefore not recommended.

Concomitant administration of SEEBRI BREEZHALER and orally inhaled indacaterol, a beta2-adrenergic agonist, under steady-state conditions of both medicines did not affect the pharmacokinetics of either medicine.

Although no formal drug interactions studies have been performed, SEEBRI BREEZHALER has been used concomitantly with other medicines commonly used in the treatment of COPD without clinical evidence of medicine interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids.

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport, increased total exposure (AUC) to glycopyrronium by 22 % and decreased renal clearance by 23 %. Based on the magnitude of these changes, no clinically relevant medicine 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 medicines, nor processes involving medicine transporters. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see *Pharmacokinetc properties – Biotransformation/metabolism and Elimination*). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the medicine.

4.6 Fertility, pregnancy and lactation

Safety has not been demonstrated in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

SEEBRI BREEZHALER may have an influence on the ability of patients to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue, dizziness or vertigo during treatment with SEEBRI BREEZHALER (see section 4.8).

4.8 Undesirable effects

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 1 353 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 characterised by symptoms related to anticholinergic effects. Adverse medicine 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 which included 1 075 patients 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); rare (≥ 1/10 000, <1/ 1 000); very rare (<1/10 000), including isolated reports.

Table 1: Adverse drug reactions in pooled COPD safety database

Adverse medicine reactions	**Glycopyrronium bromide 50 µg 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	8 (0. 7)	2 (0. 4)	uncommon
- Sinus congestion	7 (0. 7)	1 (0. 2)	uncommon
- Productive cough	6 (0. 6)	1 (0. 2)	uncommon
- Throat irritation	3 (0. 3)	1 (0. 2)	uncommon
- Epistaxis			
Infections and infestations			
- Rhinitis	8 (0. 7)	2 (0. 4)	uncommon
- Cystitis	3 (0. 3)	0 (0)	uncommon

Metabolism and nutrition disorders - Hyperglycaemia	8 (0. 7)	2 (0. 4)	uncommon
Renal and urinary disorders - Dysuria - Urinary retention	7 (0. 7) 2 (0. 2)	1 (0. 2) 0 (0)	uncommon uncommon
Cardiac disorders - Atrial fibrillation - Palpitations	6 (0. 6) 2 (0. 2)	0 (0) 0 (0)	uncommon uncommon
Nervous system disorders - Hypoaesthesia	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

Special populations

In elderly patients above 75 years of age the frequency 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions allows continued monitoring of the benefit/risk balance of SEEBRI BREEZHALER. Healthcare professionals are asked to report any suspected adverse reactions via patientsafety.sacg@novartis.com and via the "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA`s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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 (glycopyrrolate) (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.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC

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

5.1 Pharmacodynamic properties

Glycopyrronium bromide (glycopyrrolate) is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic) which blocks the action of acetylcholine on airway smooth muscle cells.

Of the five known muscarinic receptor subtypes (M1-5), only subtypes M1-3 have a defined physiological function in the human lung. Glycopyrronium bromide (glycopyrrolate) is a muscarinic receptor antagonist of subtypes M1-3. It demonstrated 4- to 5-fold selectivity for the human M3 and M1 receptors over the human M2 receptor in competition binding studies.

The duration of action can be partly attributed to the prolonged terminal elimination half-life of glycopyrronium after inhalation (*see Pharmacokinetic Properties - Elimination*).

5.2 Pharmacokinetic properties

Absorption

Following oral inhalation 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 apparent volume of distribution (Vss) of glycopyrronium was 83 L and the apparent volume of distribution in the terminal phase (Vz) was 376 L. Following inhalation, the apparent volume of distribution in the terminal phase (Vz/F) was 7 310 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 (glycopyrrolate) 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 catalysed 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 medicine. Since *in vitro* studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4 % of parent medicine Cmax and AUC) after i.v. administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide (glycopyrrolate) 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.

In vitro inhibition studies demonstrated that glycopyrronium bromide (glycopyrrolate) 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 (glycopyrrolate) 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 (glycopyrrolate) 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.

Renal elimination of parent medicine 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 medicine.

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 *Pharmacokinetic properties – 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 (glycopyrrolate). A 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.

6 PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS:

Capsule fill: Lactose monohydrate, magnesium stearate.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store at or below 25 ºC and protect from moisture.

The capsules must be kept in the blister until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

Aluminium foil blisters made of silver forming foil (polyamide /aluminium/polyvinyl chloride) sealed to a white backing foil (polyethylene terephthalate/aluminium).

Each blister strip containing 6 or 10 capsules per blister is enclosed in a cardboard carton with 1 inhaler device.

Pack sizes: 10, 12, 30, 90 or 150 capsules with 1 inhaler (Not all pack sizes may be marketed).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for handling and use

Please read the full **Instructions for Use** before using the **SEEBRI BREEZHALER®**.



Insert



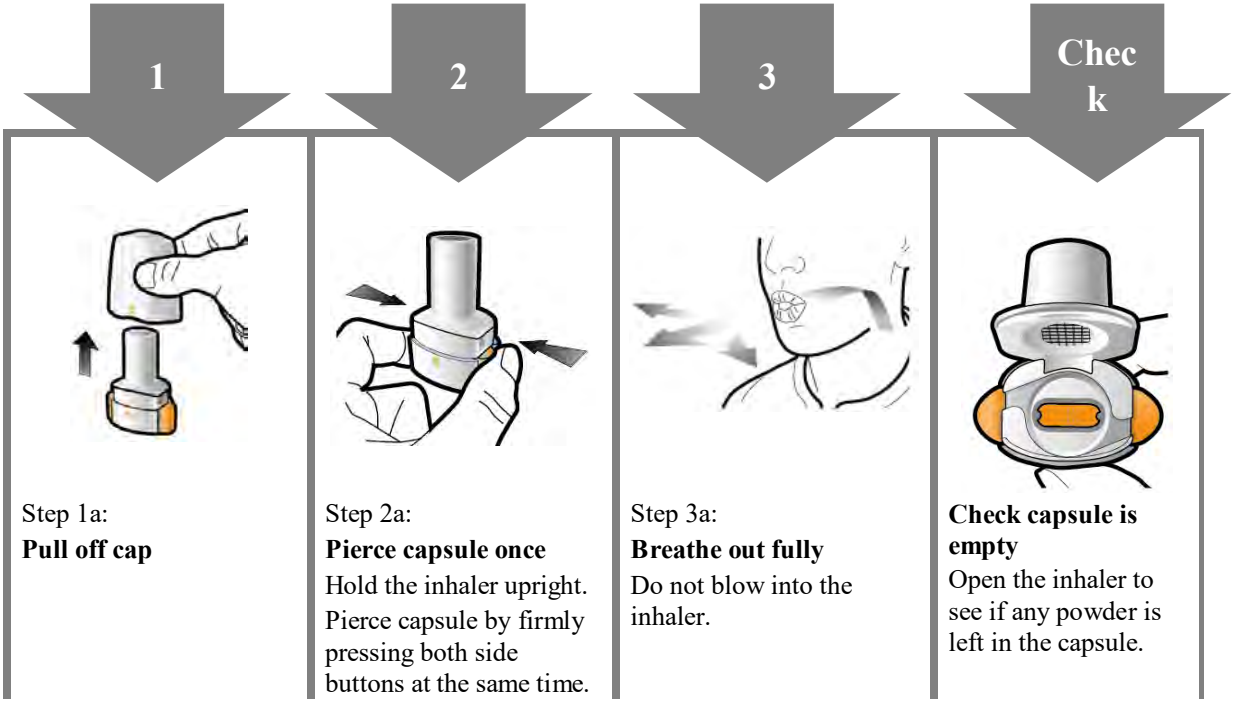
Pierce and release



Inhale deeply



Check capsule is empty



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.

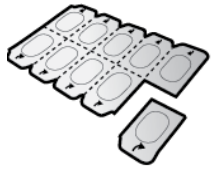
Step 3a:
Breathe out fully
Do not blow into the inhaler.

Check capsule is empty
Open the inhaler to see if any powder is left in the capsule.



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 1d:

Insert capsule

Never place a capsule directly into the mouthpiece.

You should hear a noise as the capsule is pierced.

Only pierce the capsule once.



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.

Do not press the side buttons.

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.

If there is powder left in the capsule:

Close the inhaler.

Repeat steps 3a to 3c.



Powder

Em

pty

remaining



Remove empty capsule

Put the empty capsule in your household waste.

Close the inhaler and replace the cap.

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



Step 1e:
Close inhaler

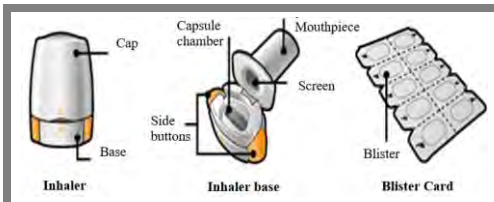
foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the **SEEBRI BREEZHALER®** capsules with any other inhaler.
- Do not use the **SEEBRI BREEZHALER®** inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- 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.

Your **SEEBRI BREEZHALER®** Inhaler pack contains:
- One **SEEBRI BREEZHALER®** inhaler
- One or more blister cards, each containing either 6 or 10 **SEEBRI BREEZHALER®** capsules to be used in the inhaler

Frequently Asked Questions

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

Cleaning the inhaler
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.

<table>
<tr>
<td>
</td>
<td>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.</td>
<td>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.</td>
</tr>
</table>

7 MARKETING AUTHORISATION HOLDER

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

8 MARKETING AUTHORISATION NUMBER(S)

46/10.2.1/0840

9 DATE OF FIRST AUTHORISATION

06 August 2015

10 DATE OF REVISION OF THE TEXT

18 August 2020

Namibia: 15/10.2/0154	NS1
Botswana: BOT1803318A	S2

Tracking Numbers:

2012-PSB/GLC-0563s, 2013-PSB/GLC-0660s, 2014-PSB/GLC-0726s, 2016-PSB/GLC-0810s