SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT
SEBRALER 50 mcg Capsule with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Glycopyrronium bromide…….63 micrograms (equivalent to 50 micrograms glycopyrronium)
Each delivered dose (the dose that leaves the mouthpiece of the SEBRALER) 44 micrograms glycopyrronium

Excipients:
Lactose monohydrate (derived from bovine milk) ..... 25.5 mg
Sunset yellow FCF-FD&C Yellow 6 ..... 0.188 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Inhalation capsule
Orange colored transparent No.3 capsules containing homogeneous powder mixture

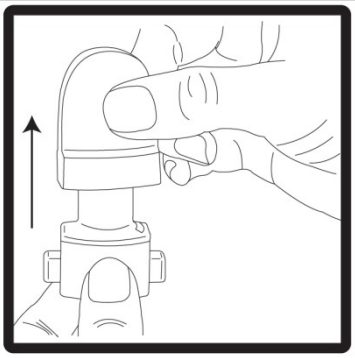
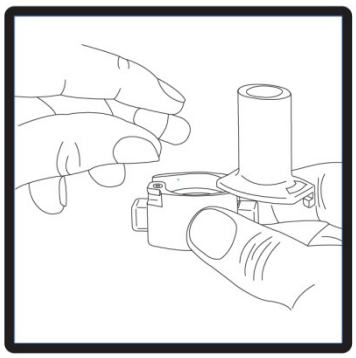
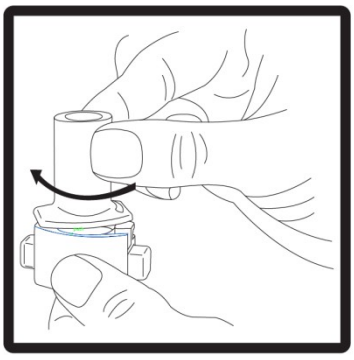
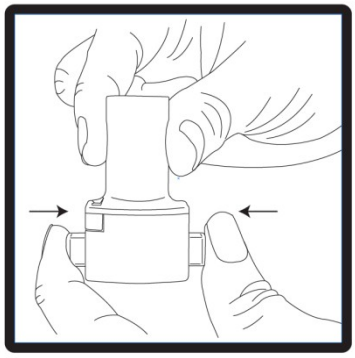
4. CLINICAL PARTICULARS
4.1. Therapeutic indications
When SEBRALER is used regularly in moderate and severe COPD (chronic obstructive pulmonary disease) cases, it reduces the frequency of attacks, improves symptoms and quality of life; however, it does not change the long-term FEV1 decline.

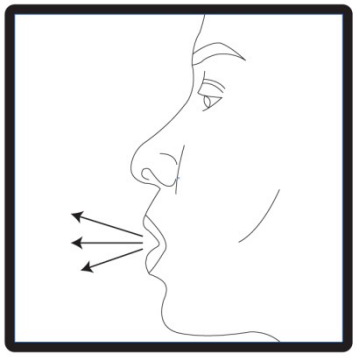
4.2. Posology and method of administration
Posology/ Frequency and duration of administration:
The recommended dose is the inhalation of the content of one capsule of 50 micrograms once daily using the SEBRALER inhaler.

Method of administration:
SEBRALER capsules should only be administered by oral inhalation using the SEBRALER inhaler. SEBRALER capsules should not be swallowed (See Section 4.9).
SEBRALER is recommended to be administered once a day 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 use more than one dose per day.

SEBRALER capsules must always be stored in the blister in order to protect from moisture and must only be removed from blister IMMEDIATELY BEFORE USE.

When prescribing SEBRALER, patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicinal product rather than inhaling it.

	1.Pull off the cap.
	2. While holding the bottom of the device firmly, open the mouthpiece by turning it in the direction of the arrow.
	3. Remove the capsule from its packaging just before use. Insert a capsule into the capsule-shaped chamber at the base of the device.
	4. Turn the mouthpiece to the closed position.
	5. Hold the device upright (mouthpiece up) and simultaneously press the side buttons ONLY ONCE. In this way, leave the edge protrusions after the capsule is pierced. Attention please: During this procedure, the gelatin capsule may break apart and there is a possibility that small pieces of gelatin may get into the mouth and throat during inhalation. Pieces of gelatin are harmless and are digested after ingestion. Unpacking the

	capsule just before use and pressing the side buttons only once to pop the capsule minimizes the risk of the gelatin capsule breaking apart (see step 3).
	6. Exhale forcefully.
	7. Place the mouthpiece in your mouth and tilt your head back slightly. Close your lips tightly around the mouthpiece and inhale as quickly and deeply as you can. As the powder disperses, you will hear a "buzz" sound caused by the capsule spinning in its compartment. If you have not heard this sound, it may be stuck in the capsule compartment. In this case, open the device and loosen the capsule by moving it in its compartment. DO NOT press the buttons more than once to loosen the capsule.
8. Hold breath: While removing the inhaler from your mouth, hold your breath for 5-10 seconds or as long as possible. Then exhale. Turn on the inhaler to check for any powder remaining in the capsule. If powder remains in the capsule, turn off the inhaler and repeat steps 9, 10, 11 and 12. Most patients can empty the capsule in one or two inhalations. Some people rarely cough for a short time after taking the drug by inhalation. If you cough, do not worry. As long as the capsule is empty, you will have taken the full dose of your medicine.	
9. After use, discard the empty capsule and close the mouthpiece.	

Additional information:
Rarely, small particles of the capsule may pass through the sieve into your mouth. In this case, you can feel the particles on your tongue. These particles are not harmful if swallowed or inhaled. If the capsule is punctured more than once (see Step 7) there will be an increased possibility of rupture of the capsule.

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

Additional information for special populations:
Renal impairment
SEBRALER 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, SEBRALER should only be used if the expected benefits outweigh the potential risk (see sections 4.4 and 5).

Hepatic impairment
Specific studies have not been conducted in patients with hepatic impairment. Since SEBRALER is primarily cleared by renal excretion, no increase in exposure is expected in patients with hepatic impairment.

Paediatric population
SEBRALER should not be used in patients under 18 years of age.

Elderly population
SEBRALER can be used at the recommended dose in elderly patients 75 years and older.

4.3. Contraindications
SEBRALER is contraindicated in hypersensitivity to active substance or to any of the excipients of the product.

4.4. Special warnings and precautions for use
Not for acute use.

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

Hypersensitivity:
Immediate hypersensitivity reactions have been reported after administration of glycopyrronium bromide. 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, SEBRALER treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm:
As with other inhalation therapies, administration of SEBRALER can result in paradoxical bronchospasm, which can be life threatening. If paradoxical bronchospasm occurs, SEBRALER treatment should be discontinued immediately and alternative therapy instituted.

Anticholinergic effect:
Like other anticholinergic drugs, SEBRALER should be used with caution in patients with narrow-angle glaucoma or urinary retention.

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

Patients with severe renal impairment:
A moderate mean increase in total systemic exposure (AUC_{last}) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end-stage renal disease.

In patients with severe renal impairment (estimated glomerular filtration rate < 30 ml/min/1.73 m^2), including those with end-stage renal disease requiring dialysis, SEBRALER should be used only if the expected benefit outweighs the potential risk (see section 5.2). These patients should be monitored closely for potential adverse 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. SEBRALER should be used with caution in these patient groups.

Lactose:
SEBRALER contains 25.5 mg of lactose in each capsule.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

SEBRALER may cause allergic reactions due to the sunset yellow FCF-FD&C yellow 6 it contains.

4.5. Interaction with other medicinal products and other forms of interaction
The co-administration of glycopyrronium bromide with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended.

Although no formal drug interaction studies have been performed, glycopyrronium bromide has been used concomitantly with other medicinal products commonly used in the treatment of COPD without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, and oral or inhaled steroids.

Co-administration of glycopyrronium bromide and orally administered inhaled indacaterol, a beta2-adrenergic agonist, under steady-state conditions for both drugs did not affect the pharmacokinetics of either drug.

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 glycopyrronium is co-administered with cimetidine or other inhibitors of organic cation transport.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: C

Woman of child-bearing potential / Contraception
No data is available.

Pregnancy
Animal studies are inconclusive regarding effects on pregnancy/and-or/embryonic/fetal development/and-or/partum/and-or/postnatal development (see section 5.3). The potential risk for humans is unknown. SEBRALER should not be used during pregnancy unless necessary.

There are no clinical studies of exposed pregnancies in COPD patients. Glycopyrronium bromide was not teratogenic in rabbits or rats following inhalation administration (see section 5.3). Umbilical plasma concentrations are low 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide in humans who have had a cesarean delivery. Due to the lack of experience in pregnant women, SEBRALER should be used during pregnancy only if the benefits to the patient justify the potential risk to the foetus.

Breast-feeding
It is unknown whether glycopyrronium is excreted in human milk. However, glycopyrronium bromide (including its metabolites) is excreted in the milk of lactating rats. Use of SEBRALER by breastfeeding women should only be considered when the expected benefit to the woman outweighs the potential risk to the infant (see section 5.3).

Reproductive ability / Fertility
Reproduction studies and other data in animals do not indicate a concern regarding fertility in either males or females (see section 5.3).

4.7. Effects on ability to drive and use machines
SEBRALER has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects
Summary of the safety profile:
The most common anticholinergic adverse reaction was dry mouth (2.4%). The majority of the reports of dry mouth were suspected to be related to the medicinal product and were mild, with none being severe.

The safety profile is further characterised by other symptoms related to the anticholinergic effects, including signs of urinary retention, which were uncommon. Gastrointestinal effects including gastroenteritis and dyspepsia were also observed. Adverse reactions related to local tolerability included throat irritation, nasopharyngitis, rhinitis and sinusitis. At the recommended dose, SEBRALER has no effects on blood pressure and heart rate.

Summary of adverse reactions observed in clinical studies:
Adverse reactions reported during the first six months of two pooled pivotal Phase III trials of 6 and 12 months duration are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to, <1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000), not known (cannot be estimated from the available data).

Infections and infestations
Common: Nasopharyngitis[1]
Uncommon: Rhinitis, cystitis

Immune system disorders
Uncommon: Hypersensitivity, angioedema[2]

Metabolism and nutrition disorders
Uncommon: Hyperglycaemia

Psychiatric disorders
Common: Insomnia

Nervous system disorders
Common: Headache[3]
Uncommon: Hypoesthesia

Cardiac disorders
Uncommon: Atrial fibrillation, palpitations

Respiratory, thoracic and mediastinal disorders
Uncommon: Sinus congestion, productive cough, throat irritation, epistaxis, dysphonia
Not known: Paradoxical bronchospasm[2]

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

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus[2].

Musculoskeletal and connective tissue disorders
Common: Musculo-skeletal pain
Uncommon: Pain in extremity, musculo-skeletal chest pain

Renal and urinary disorders
Common: Urinary tract infection[3]
Uncommon: Dysuria, urinary retention

General disorders and administration site conditions
Uncommon: Fatigue, asthenia

1 More frequent for glycopyrronium bromide than placebo in the 12 months trial.

[2]Reports have been received from post-approval marketing experience in association with the use of glycopyrronium bromide. These were reported voluntarily from a population of uncertain size, and it is therefore not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Therefore the frequency was calculated from clinical trial experience.
[3]Seen more frequently for glycopyrronium than placebo in elderly >75 years only

In the pooled 6-month database the frequency of dry mouth was 2.2% versus 1.1%, of insomnia 1% versus 0.8%, and of gastroenteritis 1.4% versus 0.9%, for glycopyrronium bromide and placebo respectively.

Dry mouth was reported mainly during the first 4 weeks of treatment with a median duration of four weeks in the majority of patients. However in 40% of cases symptoms continued for the entire 6- month period. No new cases of dry mouth were reported in months 7-12.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose
High doses may lead to anticholinergic signs and symptoms. Acute intoxication by inadvertent oral ingestion of SEBRALER capsules is unlikely due to the low oral bioavailability (about 5%).

Peak plasma levels and total systemic exposure following intravenous administration of 150 micrograms glycopyrronium bromide (equivalent to 120 micrograms glycopyrronium) in healthy volunteers were respectively about 50-fold and 6-fold higher than the peak and total exposure at steady-state achieved with the recommended dose (44 micrograms once daily) of glycopyrronium bromide and were well tolerated.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for obstructive airway diseases, anticholinergics,
ATC code: R03BB06

Mechanism of action:
Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anticholinergic) 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.

Glycopyrronium bromide works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways.

Glycopyrronium bromide is a high affinity muscarinic receptor antagonist. A greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor has been demonstrated using competitive 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 concentrations of active substance in the lung as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the Glycopyrronium bromide inhaler in contrast to the half life after intravenous administration (see section 5.2).

Pharmacodynamic effects:
The clinical Phase III development programme included two phase III studies: a 6-month placebo-controlled study and a 12-month placebo and active-controlled (open label tiotropium 18 micrograms once daily) study, both in patients with clinical diagnosis of moderate to severe COPD.

Effects on lung function
Glycopyrronium 50 micrograms once daily provided consistently statistically significant improvement in lung function (forced expiratory volume in one second, FEV_1, forced vital capacity, FVC, and inspiratory capacity, IC) in a number of clinical studies. In phase III studies, bronchodilator effects were seen within 5 minutes after the first dose and were maintained over the 24-hour dosing interval from the first dose. There was no attenuation of the bronchodilator effect over time in the 6- and 12-month studies. The magnitude of the effect 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), glycopyrronium increased trough FEV_1 by 72 ml in patients with the lowest degree of reversibility (<5%) and by 113 ml in those patients with a higher degree of reversibility at baseline (≥5%) compared to placebo (both $p<0.05$).

In the 6-month study, Glycopyrronium increased FEV_1 after the first dose with an improvement of 93 ml within 5 minutes and 144 ml within 15 minutes of dosing, compared to placebo (both *p<0,001*).

In the 12-month study, the improvements were 87 ml at 5 minutes and 143 ml at 15 minutes (both *p<0,001*). In the 12-month study, Glycopyrronium, produced statistically significant improvements in FEV_1 compared to tiotropium in the first 4 hours after dosing on day 1 and at week 26, and numerically greater values for FEV_1 in the first 4 hours after dosing than tiotropium at week 12 and week 52.

The values for FEV_1 at the end of the dosing interval (24 h post dose) were similar between the first dose and those seen after 1 year of dosing. At 12 weeks (primary endpoint), Glycopyrronium increased trough FEV_1 by 108 ml in the 6-month study and by 97 ml in the 12-month study compared to placebo (both *p<0.001*) In the 12-month study, the improvement in tiotropium compared to placebo was 83 ml (*p<0.001*).

Symptomatic outcomes
Glycopyrronium administered at 50 micrograms once daily statistically significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI). In a pooled analysis of the 6- and 12-month pivotal studies a statistically significantly higher percentage of patients receiving Glycopyrronium bromide responded with a 1 point or greater improvement in the TDI focal score at week 26 compared to placebo (58.4% and 46.4% respectively, *p<0.001*).

Glycopyrronium once daily has also shown a statistically significant effect on health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ). A pooled analysis of the 6- and 12-month pivotal studies found a statistically significantly higher percentage of patients receiving Glycopyrronium responded with a 4 point or greater improvement in SGRQ compared to placebo at week 26 (57.8% and 47.6% respectively,

p<0,001). For patients receiving tiotropium, 61.0% responded with a 4 point or greater improvement in SGRQ (p=0.004 compared to placebo).

COPD exacerbations reduction
COPD exacerbation data was collected in the 6- and 12–month pivotal studies. In both studies, the percentage of patients experiencing a moderate or severe exacerbation (defined as requiring treatment with systemic corticosteroids and/or antibiotics or hospitalisation) was reduced. In the 6-month study, the percentage of patients experiencing a moderate or severe exacerbation was 17.5% for Glycopyrronium and 24.2% for placebo (Hazard ratio: 0.69, p=0.023), and in the 12-month study it was 32.8% for Glycopyrronium and 40.2% for placebo (Hazard ratio: 0.66, p=0.001). In a pooled analysis of the first 6 months of treatment in the 6- and 12-month studies, compared to placebo Glycopyrronium statistically significantly prolonged time to first moderate or severe exacerbation and reduced the rate of moderate or severe COPD exacerbations (0.53 exacerbations/year versus 0.77 exacerbations /year, p<0,001). The pooled analysis also showed fewer patients treated with Glycopyrronium than with placebo experienced an exacerbation requiring hospitalisation (1.7% versus 4.2%, p=0.003)

Other effects
Glycopyrronium once daily statistically significantly reduced the use of rescue medication (salbutamol) 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

In a 3-week study where exercise tolerance was tested via cycle ergometer at submaximal (80%) workload (submaximal exercise tolerance test), Glycopyrronium, dosed in the morning, reduced dynamic hyperinflation and improved the length of time exercise could be maintained from the first dose onwards. On the first day of treatment inspiratory capacity under exercise was improved by 230 ml and exercise endurance time was improved by 43 seconds (an increase of 10%) compared to placebo. After three weeks of treatment the improvement in inspiratory capacity with glycopyrroniu Sebraler 50 mcg inhalation powder,capsule was similar to the first day (200 ml), exercise endurance time however had increased by 89 seconds (an increase of 21%) compared to placebo. Glycopyrronium was found to decrease dyspnoea and leg discomfort when exercising as measured using Borg scales. Glycopyrronium also reduced dyspnoea at rest measured using the Transitional Dyspnoea Index.

Secondary pharmacodynamic effects
No change in mean heart rate or QTc interval was observed with glycopyrronium in doses up to 176 micrograms in COPD patients. In a thorough QT study in 73 healthy volunteers, a single inhaled dose of glycopyrronium 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. The effect on heart rate and QTc interval of 150 micrograms glycopyrronium bromide (equivalent to 120 micrograms glycopyrronium) administered intravenously was investigated in young healthy subjects. Peak exposures (C_{max}) about 50-fold higher than after inhalation of glycopyrronium 44 micrograms at steady state were achieved and did not result in tachycardia or QTc prolongation. A slight reduction in heart rate (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, was observed.

<u>Paediatric population</u>
The European Medicines Agency has waived the obligation to submit the results of studies with

glycopyrronium in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use)

5.2. Pharmacokinetic properties

Absorption:

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

The absolute bioavailability of glycopyrronium inhaled through the glycopyrronium bromide inhaler has been calculated to be approximately 45% over the mouthpiece dose of 44 micrograms. 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 has been calculated to be approximately 5%.

In patients with COPD, pharmacokinetic steady-state of glycopyrronium was reached within one week of the start of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium for a 44 micrograms once-daily dosing regimen were 166 picograms/ml and 8 picograms/ml, respectively. Steady-state exposure to glycopyrronium (AUC over the 24-hour dosing interval) was about 1.4- to 1.7-fold higher than after the first dose.

Distribution:

After i.v. dosing, the steady-state volume of distribution (Vss) of glycopyrronium is 83 L and the volume of distribution in the terminal phase (Vz) is 376 L. The apparent volume of distribution in the terminal phase following inhalation was almost 20-fold larger, which reflects the much slower elimination after inhalation. The *in vitro* human plasma protein binding of glycopyrronium is 38% to 41% at concentrations of 1 to 10 nanograms/ml.

Biotransformation:

In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide between animals and humans. 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 vivo*, M9 is formed from the swallowed dose fraction of inhaled glycopyrronium bromide. 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 metabolism studies showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. Inhibition or induction of the metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the active substance.

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 OCT1 or OCT2. *In vitro* enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide for cytochrome P450 isoenzymes, or for UGT1A1 and the transporters MDR1 and MRP2.

Elimination:
After intravenous administration of [^{3}H]-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. The mass balance is therefore almost exact.

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.

Mean renal clearance of glycopyrronium following inhalation was in the range of 17.4 and 24.4 litres/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20% of a 50 microgram dose was detected in the urine as the 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 the systemic circulation at and beyond 24 hours after inhalation.

Linearity/non-linearity:
In COPD patients both systemic exposure and total urinary excretion of glycopyrronium at pharmacokinetic steady state increased about dose-proportionally over the dose range of 44 to 176 micrograms when evaluated over the mouthpiece dose of 44 micrograms.

Characteristic in patients
Hepatic impairment:
Clinical studies have not been conducted in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion (see Section 5.2). Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure.

Renal impairment:
Renal impairment has an impact on the systemic exposure to glycopyrronium bromide. A moderate mean increase in total systemic exposure (AUC_{last}) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end-stage renal disease.

Using a population pharmacokinetics analysis, it was concluded that Glycopyrronium bromide can be used at the recommended dose in COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate, eGFR ≥30 ml/min/1.73 m^2).

In patients with severe renal impairment, including end-stage renal disease requiring dialysis (calculated glomerular filtration rate eGFR <30 ml/min/1.73 m^2), SEBRALER should only be used if the expected benefit outweighs the potential risk (see section 4.4).

Pediatric population:
Since COPD is an indication for only adults, SEBRALER should not be used in patients under 18 years of age.

Elderly population:
SEBRALER, can be used at the recommended dose in elderly patients 75 years of age and older.

Age, gender, body weight, race:
A population pharmacokinetic analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure.
Once a day SEBRALER can be used safely in all age and body weight groups.

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

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

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

Effects observed during repeated dose inhalation toxicity studies were attributed to mild local irritation or exacerbations of the expected pharmacological action of glycopyrronium bromide. These include mild to moderate increases in heart rate in dogs and a range of reversible changes associated with decreased secretion of saliva, lacrimal and Harder glands and pharynx in rats and dogs. Lens opacities observed during chronic studies in rats have been described for other muscarinic antagonists and are considered to be species-specific changes of limited importance for their therapeutic use in patients. Findings in the respiratory tract of rats included degenerative/regenerative changes in the nasal cavity and larynx with inflammation consistent with mild local irritation.

Minimal epithelial changes were also observed at the bronchioloalveolar junction of the lung in rats, which were considered a mild adaptive response. All of these findings are of limited relevance during clinical use, as they were observed at exposures considered greater than the maximum human exposure.

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 micrograms once daily for humans.

Published data for glycopyrronium bromide indicate no reproductive toxicity problems. Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Reproductive studies in rats and other animal data did not raise a fertility concern in either male or female 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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (derived from bovine milk)
Capsule content:
Sunset yellow FCF-FD&C Yellow 6
Hypromellose

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store in room temperature below 25ºC.
Protect from moisture.

6.5. Nature and contents of container

Blister consisting of OPA-Alu-PVC foil and aluminum foil was used as the primary packaging material. Blisters are presented within a cardboard box, in a separator, with a monodose dry powder inhaler device and patient information leaflet. Each cardboard box contains 3 blisters, each blister contains 10 capsules or 9 blisters, each blister contains 10 capsules and 1 device (Monodose dry powder inhaler) in a plastic separator.

Each cardboard box contains 30 or 90 orange colored HPMC capsules and 1 dry powder inhaler device in a plastic separator.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece - İSTANBUL/TÜRKİYE

8. MARKETING AUTHORISATION NUMBER

2018/468

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31.08.2018
Date of renewal:

10. DATE OF REVISION OF THE TEXT