ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Enurev Breezhaler 44 micrograms inhalation powder, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 63 micrograms of glycopyrronium bromide equivalent to 50 micrograms of glycopyrronium.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 micrograms of glycopyrronium bromide equivalent to 44 micrograms of glycopyrronium.

Excipient(s) with known effect:
Each capsule contains 23.6 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule (inhalation powder).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enurev Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology
The recommended dose is the inhalation of the content of one capsule once daily using the Enurev Breezhaler inhaler.

Enurev Breezhaler is recommended to be administered, 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.

Special populations
Elderly population
Enurev Breezhaler can be used at the recommended dose in elderly patients (75 years of age and older) (see section 4.8).

Renal impairment
Enurev Breezhaler can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis Enurev Breezhaler should be used only if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrronium may be increased in this population (see sections 4.4 and 5.2).

Hepatic impairment
No studies have been conducted in patients with hepatic impairment. Glycopyrronium is predominantly cleared by renal excretion and therefore no major increase in exposure is expected in patients with hepatic impairment. No dose adjustment is required in patients with hepatic impairment.

Paediatric population
There is no relevant use of Enurev Breezhaler in the paediatric population (under 18 years) in the indication COPD.

Method of administration
For inhalation use only.

The capsules must be administered only using the Enurev Breezhaler inhaler (see section 6.6).

The capsules must only be removed from the blister immediately before use.

The capsules must not be swallowed.

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.

For instructions on use of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Not for acute use
Enurev Breezhaler 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 Enurev 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, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm
In clinical studies with Enurev Breezhaler, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life-threatening. If this occurs, treatment should be discontinued immediately and alternative therapy instituted.

Anticholinergic effect
Enurev Breezhaler 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 Enurev Breezhaler 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 below 30 ml/min/1.73 m^2), including those with end-stage renal disease requiring dialysis, Enurev Breezhaler 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. Enurev Breezhaler should be used with caution in these patient groups.

Excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The co-administration of Enurev Breezhaler with other anticholinergic-containing medicinal products has not been studied and is therefore not recommended.

Although no formal drug interaction studies have been performed, Enurev Breezhaler 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 and inhaled steroids.

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.

Concomitant administration of glycopyrronium and orally inhaled indacaterol, a $beta_2$-adrenergic agonist, under steady-state conditions of both active substances did not affect the pharmacokinetics of either medicinal product.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Enurev Breezhaler in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Glycopyrronium should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding
It is unknown whether glycopyrronium bromide is excreted in human milk. However, glycopyrronium bromide (including its metabolites) was excreted in the milk of lactating rats (see section 5.3). The use of glycopyrronium by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant (see section 5.3).

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

Glycopyrronium 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.

Tabulated summary of adverse reactions
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 (Table 1). 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: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions

Adverse reactions	Frequency category
Infections and infestations	
Nasopharyngitis[1)]	Common
Rhinitis	Uncommon
Cystitis	Uncommon
Immune system disorders	
Hypersensitivity	Uncommon
Angioedema[2)]	Uncommon
Metabolism and nutrition disorders	
Hyperglycaemia	Uncommon
Psychiatric disorders	
Insomnia	Common
Nervous system disorders	
Headache[3)]	Common
Hypoaesthesia	Uncommon
Cardiac disorders	
Atrial fibrillation	Uncommon
Palpitations	Uncommon

Respiratory, thoracic and mediastinal disorders	
Sinus congestion	Uncommon
Productive cough	Uncommon
Throat irritation	Uncommon
Epistaxis	Uncommon
Dysphonia[2)]	Uncommon
Paradoxical bronchospasm[2)]	Not known
Gastrointestinal disorders	
Dry mouth	Common
Gastroenteritis	Common
Nausea[2)]	Uncommon
Vomiting[1) 2)]	Uncommon
Dyspepsia	Uncommon
Dental caries	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Pruritus[2)]	Uncommon
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain[1) 2)]	Common
Pain in extremity	Uncommon
Musculoskeletal chest pain	Uncommon
Renal and urinary disorders	
Urinary tract infection[3)]	Common
Dysuria	Uncommon
Urinary retention	Uncommon
General disorders and administration site conditions	
Fatigue	Uncommon
Asthenia	Uncommon

1) More frequent for glycopyrronium than placebo in the 12 months database only.
2) Reports have been received from post-approval marketing experience in association with the use of Enurev Breezhaler. 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.

Description of selected adverse reactions
In the pooled 6-month database the frequency of dry mouth was 2.2% versus 1.1%, of insomnia 1.0% versus 0.8%, and of gastroenteritis 1.4% versus 0.9%, for Enurev Breezhaler 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 listed in Appendix V.

4.9 Overdose

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

Acute intoxication by inadvertent oral ingestion of Enurev Breezhaler 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 Enurev Breezhaler 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 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 radioligand 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 Enurev Breezhaler 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
Enurev Breezhaler 44 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), Enurev Breezhaler 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, Enurev Breezhaler 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, Enurev Breezhaler 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), Enurev Breezhaler 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 versus placebo for tiotropium was 83 ml (p<0.001).

Symptomatic outcomes
Enurev Breezhaler administered at 44 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 Enurev Breezhaler 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). These findings were similar to those seen in patients receiving tiotropium, 53.4% of whom responded with 1 point or greater improvement (p=0.009 compared to placebo).

Enurev Breezhaler 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 Enurev Breezhaler 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 Enurev Breezhaler and 24.2% for placebo (Hazard ratio: 0.69, p=0.023), and in the 12-month study it was 32.8% for Enurev Breezhaler 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 Enurev Breezhaler 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 0.77exacerbations /year, p<0.001). The pooled analysis also showed fewer patients treated with Enurev Breezhaler than with placebo experienced an exacerbation requiring hospitalisation (1.7% versus 4.2%, p=0.003).

Other effects
Enurev Breezhaler 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), Enurev Breezhaler, 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 Enurev Breezhaler was similar to the first day (200 ml), exercise endurance time however had increased by 89 seconds (an increase of 21%) compared to placebo. Enurev Breezhaler was found to decrease dyspnoea and leg discomfort when exercising as measured using Borg scales. Enurev Breezhaler 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 Enurev Breezhaler 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Enurev Breezhaler 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 Enurev Breezhaler inhaler, glycopyrronium was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of glycopyrromium inhaled via Enurev Breezhaler was estimated to be about 45% of the delivered dose. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption.

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 intravenous dosing, the steady-state volume of distribution of glycopyrronium was 83 litres and the volume of distribution in the terminal phase was 376 litres. 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 was 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.

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.

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 23% of the delivered dose was found in urine as parent drug.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests 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.

Special populations
A population pharmacokinetic analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Enurev Breezhaler 44 micrograms 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.

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.

Patients with hepatic impairment
Clinical studies have not been conducted in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion. Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure.

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

filtration rate, eGFR ≥30 ml/min/1.73 m^2) Enurev Breezhaler can be used at the recommended dose. In patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2), including those with end-stage renal disease requiring dialysis, Enurev Breezhaler should only be used if the expected benefit outweighs the potential risk (see section 4.4).

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 attributable to the muscarinic receptor antagonist properties of glycopyrronium bromide included mild to moderate increases in heart rate in dogs, lens opacities in rats and, reversible changes associated with reduced glandular secretions in rats and dogs. Mild irritancy or adaptive changes in the respiratory tract were seen in rats. All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Glycopyrronium was not teratogenic in rats or rabbits following inhalation administration. Fertility and pre- and post-natal development were not affected in rats. 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.

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 44 micrograms once daily for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate
Magnesium stearate

Capsule shell

Hypromellose
Carrageenan
Potassium chloride
Sunset yellow FCF (E110)

Printing ink

Shellac (E904)
Propylene glycol
Ammonium hydroxide
Potassium hydroxide
Iron oxide, black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Each inhaler should be disposed of after all capsules have been used.

6.4 Special precautions for storage

Do not store above 25°C.

The capsules must always be stored in the original blister in order to protect from moisture. The capsules must only be removed immediately before use.

6.5 Nature and contents of container

Enurev Breezhaler is a single-dose inhaler. Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel. Each blister strip contains either 6 or 10 hard capsules.

PA/Alu/PVC – Alu perforated unit-dose blister

Packs containing 6x1, 10x1, 12x1 or 30x1 hard capsules, together with one inhaler.

Multipacks containing 90 (3 packs of 30x1) hard capsules and 3 inhalers.
Multipacks containing 96 (4 packs of 24x1) hard capsules and 4 inhalers.
Multipacks containing 150 (15 packs of 10x1) hard capsules and 15 inhalers.
Multipacks containing 150 (25 packs of 6x1) hard capsules and 25 inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

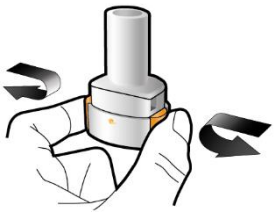
The inhaler provided with each new prescription should be used. Each inhaler should be disposed of after all capsules have been used.

Instructions for handling and use

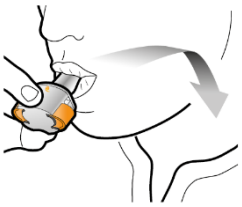
Please read the full **Instructions for Use** before using the Enurev Breezhaler.



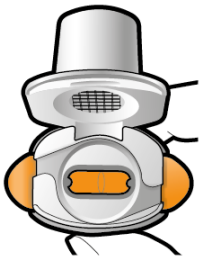
Insert



Pierce and release

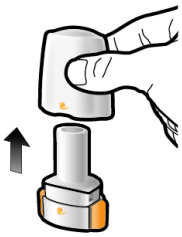


Inhale deeply

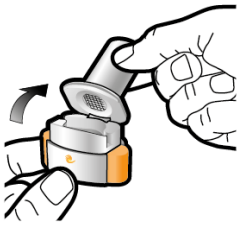


Check capsule is empty

1

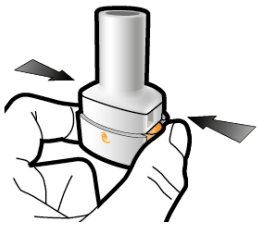


Step 1a:
Pull off cap

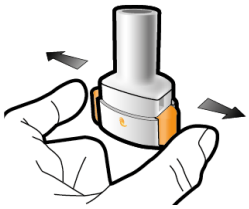


Step 1b:
Open inhaler

2



Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced.
Only pierce the capsule once.

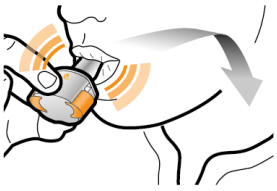


Step 2b:
Release side buttons

3

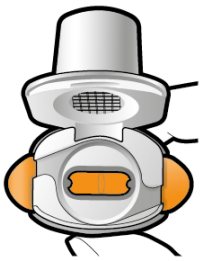


Step 3a:
Breathe out fully
Do not blow into the inhaler.



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.

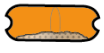
Chec k



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

If there is powder left in the capsule:

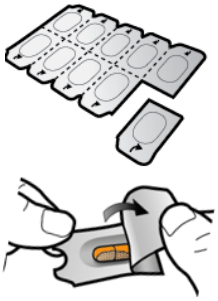
- Close the inhaler.
- Repeat steps 3a to 3c.



Powder remaining



Empty

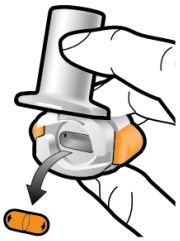


Step 1c:
Remove capsule
Separate one of the blisters from the blister card.
Peel open the blister and remove the capsule.
Do not push the capsule through the foil.
Do not swallow the capsule.

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.



Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.



Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.



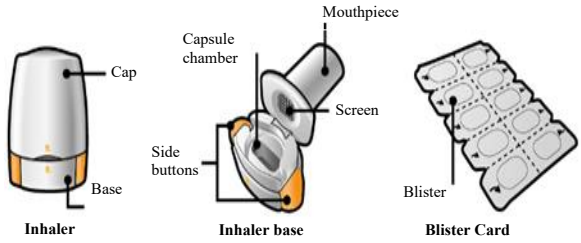
Step 1e:
Close inhaler

Important Information

- Enurev Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Enurev Breezhaler capsules with any other inhaler.
- Do not use the Enurev 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 Enurev Breezhaler Inhaler pack contains:

- One Enurev Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Enurev 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 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.

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.

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.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/789/001-008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 September 2012
Date of latest renewal: 13 July 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a signifcant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Enurev Breezhaler 44 micrograms inhalation powder, hard capsules
glycopyrronium (as glycopyrronium bromide)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 micrograms glycopyrronium. The amount of glycopyrronium delivered is 44 micrograms.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

6 x 1 capsules + 1 inhaler
10 x 1 capsules + 1 inhaler
12 x 1 capsules + 1 inhaler
30 x 1 capsules + 1 inhaler

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture. Do not remove from the blister until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/789/001	6 capsules + 1 inhaler
EU/1/12/789/007	10 capsules + 1 inhaler
EU/1/12/789/002	12 capsules + 1 inhaler
EU/1/12/789/003	30 capsules + 1 inhaler

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enurev Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Enurev Breezhaler 44 micrograms inhalation powder, hard capsules
glycopyrronium (as glycopyrronium bromide)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 micrograms glycopyrronium. The amount of glycopyrronium delivered is 44 micrograms.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Multipack: 90 (3 packs of 30 x 1) capsules + 3 inhalers.
Multipack: 96 (4 packs of 24 x 1) capsules + 4 inhalers.
Multipack: 150 (15 packs of 10 x 1) capsules + 15 inhalers.
Multipack: 150 (25 packs of 6 x 1) capsules + 25 inhalers.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture. Do not remove from the blister until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/789/004	Multipack comprising 3 packs (30 capsules + 1 inhaler)
EU/1/12/789/005	Multipack comprising 4 packs (24 capsules + 1 inhaler)
EU/1/12/789/008	Multipack comprising 15 packs (10 capsules + 1 inhaler)
EU/1/12/789/006	Multipack comprising 25 packs (6 capsules + 1 inhaler)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enurev Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Enurev Breezhaler 44 micrograms inhalation powder, hard capsules
glycopyrronium (as glycopyrronium bromide)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 50 micrograms glycopyrronium. The amount of glycopyrronium delivered is 44 micrograms micrograms.

3. LIST OF EXCIPIENTS

Also contains: lactose and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

30 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.
24 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.
10 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.
6 x 1 capsules + 1 inhaler. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use only with the inhaler provided in the pack.
Do not swallow capsules.
Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
The inhaler in each pack should be disposed of after all capsules in that pack have been used.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store the capsules in the original blister in order to protect from moisture. Do not remove from the blister until immediately before use.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/789/004	Multipack comprising 3 packs (30 capsules + 1 inhaler)
EU/1/12/789/005	Multipack comprising 4 packs (24 capsules + 1 inhaler)
EU/1/12/789/008	Multipack comprising 15 packs (10 capsules + 1 inhaler)
EU/1/12/789/006	Multipack comprising 25 packs (6 capsules + 1 inhaler)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Enurev Breezhaler

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER LID OF OUTER CARTON OF UNIT PACK AND OF INTERMEDIATE CARTON OF MULTIPACK

1. OTHER

1	Insert
2	Pierce and release
3	Inhale deeply
Check	Check capsule is empty

Read the leaflet before use.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Enurev Breezhaler 44 mcg inhalation powder
glycopyrronium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Inhalation use only

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Enurev Breezhaler 44 micrograms inhalation powder, hard capsules
glycopyrronium
(as glycopyrronium bromide)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Enurev Breezhaler is and what it is used for
2. What you need to know before you use Enurev Breezhaler
3. How to use Enurev Breezhaler
4. Possible side effects
5. How to store Enurev Breezhaler
6. Contents of the pack and other information

1. What Enurev Breezhaler is and what it is used for

What Enurev Breezhaler is
This medicine contains an active substance called glycopyrronium bromide. This belongs to a group of medicines called bronchodilators.

What Enurev Breezhaler is used for
This medicine is used to make breathing easier for adult patients who have breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD).

In COPD the muscles around the airways tighten. This makes breathing difficult. This medicine blocks the tightening of these muscles in the lungs, making it easier for air to get in and out of the lungs.

If you use this medicine once a day, it will help to reduce the effects of COPD on your everyday life.

2. What you need to know before you use Enurev Breezhaler

Do not use Enurev Breezhaler
- if you are allergic to glycopyrronium bromide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before using Enurev Breezhaler, if any of the following applies to you:
- you have kidney problems.
- you have an eye problem called narrow-angle glaucoma.
- you have difficulty passing urine.

During treatment with Enurev Breezhaler, stop taking this medicine and tell your doctor immediately:
- if you experience tightness of the chest, coughing, wheezing or breathlessness immediately after using Enurev Breezhaler (signs of bronchospasm).
- if you experience difficulties in breathing or swallowing, swelling of the tongue, lips or face, skin rash, itching and hives (signs of allergic reaction).
- if you experience eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes. These may be signs of an acute attack of narrow-angle glaucoma.

Enurev Breezhaler is used as a maintenance treatment for your COPD. Do not use this medicine to treat a sudden attack of breathlessness or wheezing.

Children and adolescents
Do not give this medicine to children or adolescents below the age of 18 years.

Other medicines and Enurev Breezhaler
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines similar to Enurev Breezhaler used for your lung disease, such as ipratropium, oxitropium or tiotropium (so called anticholinergics).

No specific side effects have been reported when Enurev Breezhaler has been used together with other medicines used to treat COPD such as reliever inhalers (e.g. salbutamol), methylxanthines (e.g. theophylline) and/or oral and inhaled steroids (e.g. prednisolone).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There are no data from the use of this medicine in pregnant women and it is not known whether the active substance of this medicine passes into human milk.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines.

Enurev Breezhaler contains lactose
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use Enurev Breezhaler

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much Enurev Breezhaler to use
The usual dose is to inhale the content of one capsule each day.
You only need to inhale once a day because the effect of this medicine lasts for 24 hours.
Do not use more than your doctor tells you to use.

Elderly people
You can use this medicine if you are aged 75 years and over at the same dose as for other adults.

When to inhale Enurev Breezhaler
Use this medicine at the same time each day. This will also help you to remember to use it.

You can inhale this medicine anytime before or after food or drink.

How to inhale Enurev Breezhaler
- In this pack, you will find an inhaler and capsules (in blisters) that contain the medicine as inhalation powder. Only use the capsules with the inhaler provided in this pack (Enurev Breezhaler inhaler). The capsules should remain in the blister until you need to use them.
- Do not push the capsule through the foil.
- When you start a new pack, use the new Enurev Breezhaler inhaler that is supplied in the pack.
- Dispose of each inhaler after after all capsules in that pack have been used.
- Do not swallow the capsules.
- Please read the instructions at the end of this leaflet for more information on how to use the inhaler.

If you use more Enurev Breezhaler than you should
If you have inhaled too much of this medicine or if someone else accidentally uses your capsules, you must immediately either tell your doctor or go to the nearest emergency unit. Show the pack of Enurev Breezhaler. Medical attention may be needed.

If you forget to use Enurev Breezhaler
If you forget to inhale a dose, take one as soon as possible. However, do not take two doses on the same day. Then take the next dose as usual.

How long to continue your treatment with Enurev Breezhaler
- Keep using this medicine for as long as your doctor tells you.
- COPD is a long-term disease and you should use this medicine every day and not only when you have breathing problems or other symptoms of COPD.

If you have questions about how long to continue your treatment with this medicine, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects may be serious but are uncommon
(*may affect up to 1 in 100 people*)
- Irregular heart beat
- High level of blood sugar (hyperglycaemia: typical symptoms include excessive thirst or hunger and frequent urination)
- Rash, itching, hives, difficulty breathing or swallowing, dizziness (possible signs of allergic reaction)
- Swelling mainly of the tongue, lips, face or throat (possible signs of angioedema)

If you get any of these side effects, tell your doctor immediately.

Some side effects may be serious, but the frequency of these side effects is not known
(*frequency cannot be estimated from the available data*)
- Difficulty breathing with wheezing or coughing (signs of paradoxical bronchospasm)

Some side effects are common
(may affect up to 1 in 10 people)
- Dry mouth
- Difficulty sleeping
- Runny or stuffy nose, sneezing, sore throat
- Diarrhoea or stomach ache
- Musculoskeletal pain

Some side effects are uncommon
(may affect up to 1 in 100 people)
- Difficulty and pain when passing urine
- Painful and frequent urination
- Palpitations
- Rash
- Numbness
- Cough with sputum
- Dental caries
- Feeling of pressure or pain in the cheeks and forehead
- Nose bleeds
- Pain in arms or legs
- Pain in muscles, bones or joints of the chest
- Stomach discomfort after meals
- Throat irritation
- Tiredness
- Weakness
- Itching
- Voice alteration (hoarseness)
- Nausea
- Vomiting

Some elderly patients above 75 years of age experienced headache (frequency common) and urinary tract infection (frequency common).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Enurev Breezhaler

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.

Store the capsules in the original blister in order to protect from moisture. Do not remove from the blister until immediately before use.

The inhaler in each pack should be disposed of after all capsules in that pack have been used.

Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Enurev Breezhaler contains
- The active substance is glycopyrronium bromide. Each capsule contains 63 micrograms of glycopyrronium bromide (equivalent to 50 micrograms glycopyrronium). The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 44 micrograms of glycopyrronium.
- The other ingredients of the inhalation powder are lactose monohydrate and magnesium stearate.
- The ingredients of the capsule shell are hypromellose, water, purified, carrageenan, potassium chloride, sunset yellow FCF (E110) and printing ink.
    - The ingredients of the printing ink are shellac (E904), propylene glycol, ammonium hydroxide, potassium hydroxide and iron oxide, black (E172).

What Enurev Breezhaler looks like and contents of the pack
Enurev Breeyhaler 44 micrograms inhalation powder, hard capsules are transparent and orange and contain a white powder. They have the product code "GPL50" printed in black above and a company logo (⏻) printed in black below a black bar.

Each pack contains a device called an inhaler, together with capsules in blisters. Each blister strip contains either 6 or 10 hard capsules.

The following pack sizes are available:
Packs containing 6x1, 10x1, 12x1 or 30x1 hard capsules, together with one inhaler.

Multipacks containing 90 (3 packs of 30x1) hard capsules and 3 inhalers.
Multipacks containing 96 (4 packs of 24x1) hard capsules and 4 inhalers.
Multipacks containing 150 (15 packs of 10x1) hard capsules and 15 inhalers.
Multipacks containing 150 (25 packs of 6x1) hard capsules and 25 inhalers.

Not all pack sizes may be available in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
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Manufacturer
Novartis Farmacéutica SA
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

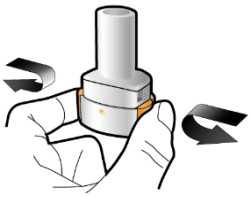
Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Instructions for use of Enurev Breezhaler inhaler

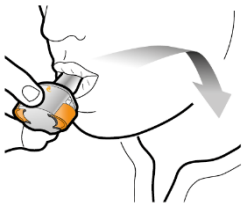
Please read the full **Instructions for Use** before using the Enurev Breezhaler.



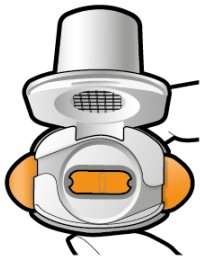
Insert



Pierce and release

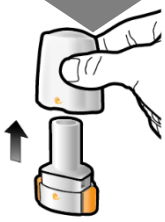


Inhale deeply

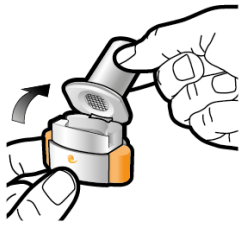


Check capsule is empty

1

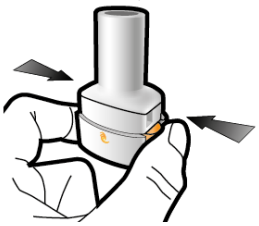


Step 1a:
Pull off cap

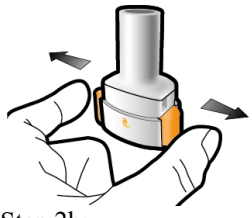


Step 1b:
Open inhaler

2



Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time. You should hear a noise as the capsule is pierced.
Only pierce the capsule once.

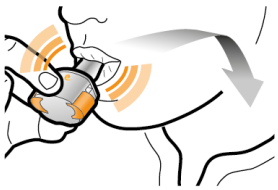


Step 2b:
Release side buttons

3

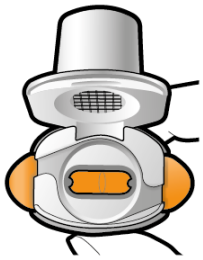


Step 3a:
Breathe out fully
Do not blow into the inhaler.



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.

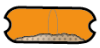
Check



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

If there is powder left in the capsule:

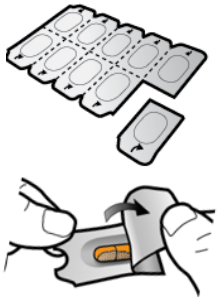
- Close the inhaler.
- Repeat steps 3a to 3c.



Powder remaining



Empty



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.

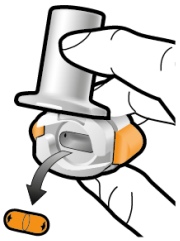


Step 1e:
Close inhaler

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.



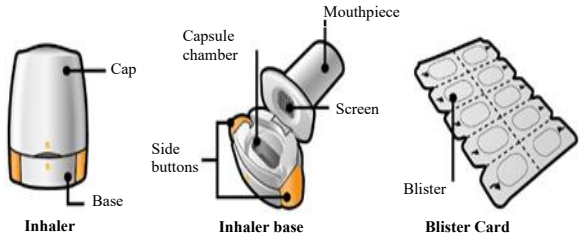
Remove empty capsule
Put the empty capsule in your household waste.
Close the inhaler and replace the cap.

Important Information

- Enurev Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Enurev Breezhaler capsules with any other inhaler.
- Do not use the Enurev 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 Enurev Breezhaler Inhaler pack contains:

- One Enurev Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 Enurev 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 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.

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.

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.