NOVARTIS

ULTIBRO BREEZHALER® (indacaterol maleate/ glycopyrronium bromide)

110/ 50 µg dry powder inhalation capsules

Professional Information

Document status: Final

Release date: 23 August 2020

SCHEDULING STATUS:

S3

1 NAME OF THE MEDICINAL PRODUCT

ULTIBRO BREEZHALER® dry powder inhalation capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains indacaterol maleate equivalent to 110 micrograms indacaterol and glycopyrronium bromide equivalent to 50 micrograms glycopyrronium.

The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 85 micrograms indacaterol and 43 micrograms glycopyrronium.

Excipients with known effect

Contains sugar: Lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule: Transparent yellow cap and transparent body capsules containing a white to practically white powder.

Imprint - Cap: " " printed in black; *Body:* "IGP110.50" printed in blue under two blue bars.

Capsule Size: 3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ULTIBRO BREEZHALER is indicated for the treatment of chronic obstructive pulmonary disease (COPD) in patients who are still symptomatic despite treatment with a long acting β2 adrenergic agonist (LABA) or a long acting muscarinic antagonist (LAMA).

4.2 Posology and method of administration

General target population

The recommended dosage of ULTIBRO BREEZHALER is the once-daily inhalation of the content of one 110/50 microgram capsule using the ULTIBRO BREEZHALER inhaler**.**

Dosing in special populations

Renal impairment

ULTIBRO BREEZHALER can be used at the recommended dose in patients with mild to moderate renal impairment. ULTIBRO BREEZHALER has not been studied in patients with severe renal impairment or end-stage renal disease requiring dialysis and no dosage recommendations can be made.

Hepatic impairment

ULTIBRO BREEZHALER can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment (see *Pharmacokinetics, Special Populations – Patients with hepatic impairment).*

Paediatrics

ULTIBRO BREEZHALER should not be used in patients under 18 years of age.

Elderly

ULTIBRO BREEZHALER can be used at the recommended dose in elderly patients 75 years of age and older without significant renal impairment.

Method of administration

ULTIBRO BREEZHALER capsules must be administered only by the oral inhalation route and only using the ULTIBRO BREEZHALER inhaler. ULTIBRO BREEZHALER capsules must not be swallowed (see *Known Symptoms of Overdosage and Particulars of its Treatment*).

ULTIBRO BREEZHALER should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day.

ULTIBRO BREEZHALER capsules must always be stored in the blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE (see *Storage Instructions*).

4.3 Contraindications

ULTIBRO BREEZHALER is contraindicated in patients with hypersensitivity to indacaterol, glycopyrronium, lactose or to any of the excipients.

4.4 Special warnings and precautions for use

ULTIBRO BREEZHALER should not be administered concomitantly with products containing other long-acting

beta-adrenergic agonists or long-acting muscarinic antagonists, medicine classes to which the components of ULTIBRO BREEZHALER belong (see *Interactions*).

Asthma

ULTIBRO BREEZHALER should not be used for the treatment of asthma.

Not for acute use

ULTIBRO BREEZHALER is not indicated for the treatment of acute episodes of bronchospasm.

Hypersensitivity related to indacaterol

Immediate hypersensitivity reactions have been reported after administration of indacaterol, one of the components of ULTIBRO BREEZHALER. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

Administration of ULTIBRO BREEZHALER may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted.

Anticholinergic effects related to glycopyrronium

ULTIBRO BREEZHALER should be used with caution in patients with narrow-angle glaucoma or urinary outflow tract obstruction e.g. due to benign prostatic hypertrophy as urinary retention may occur.

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma and of urinary outflow tract obstruction and should be informed to stop using ULTIBRO BREEZHALER and to contact their doctor immediately should any of these signs or symptoms develop.

Patients with severe renal impairment

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, have not been studied using ULTIBRO BREEZHALER. Hence the use of ULTIBRO BREEZHALER is not recommended for these patients.

Systemic effects of beta-agonists

ULTIBRO BREEZHALER should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac dysrhythmias, hypertension), in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to $beta_2$-adrenergic agonists**.** ULTIBRO BREEZHALER should not be used more often or at higher doses than recommended.

Cardiovascular effects of beta-agonists

ULTIBRO BREEZHALER may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In such cases the medicine may need to be discontinued. In addition, beta-adrenergic agonists, such as indacaterol, have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT interval and ST segment depression. The clinical significance of these findings is unknown. Therefore, long-acting beta2-adrenergic agonists (LABA) or LABA containing products such as ULTIBRO BREEZHALER should be used with caution in patients with known or suspected prolongation of the QT interval or patients treated with medicinal products affecting the QT interval.

Hypokalaemia with beta-agonists

$Beta_2$-adrenergic agonists, such as indacaterol may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see *Interactions*) which may increase the susceptibility to cardiac dysrhythmias.

Hyperglycaemia with beta-agonists

Inhalation of high doses of beta$_2$-adrenergic agonists, such as indacaterol, may produce increases in plasma glucose. Upon initiation of treatment with ULTIBRO BREEZHALER plasma glucose should be monitored more closely in diabetic patients. During clinical studies, more patients on ULTIBRO BREEZHALER experienced clinically notable changes in blood glucose (4,1 %) at the recommended dose than on placebo (2,3 %). ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled.

Lactose

ULTIBRO BREEZHALER contains lactose. Patients with the rare hereditary condition of lactose or galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose- galactose malabsorption or fructose intolerance should not use ULTIBRO BREEZHALER.

ULTIBRO BREEZHALER contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interactions linked to the ULTIBRO BREEZHALER

Concomitant administration of orally inhaled indacaterol and glycopyrronium under steady-state conditions of both medicines did not affect the pharmacokinetics (PK) of either medicine**.**

Interactions linked to indacaterol

Anticipated interactions resulting in concomitant use not being recommended

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists, such as indacaterol. Therefore ULTIBRO BREEZHALER should not be given together with beta-adrenergic blockers (including eye

drops).

Medicines known to prolong QTc interval

ULTIBRO BREEZHALER should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or medicines known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Medicines known to prolong the QT-interval may increase the risk of ventricular dysrhythmia (see *Warnings and Special Precautions*).

***Sympathomimetic* medicines**

Concomitant administration of other sympathomimetic medicines (alone or as part of combination therapy e.g. as in medicines used for colds and flu) may potentiate the undesirable effects of indacaterol (see *Warnings and Special Precautions*).

Hypokalaemia

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists, such as indacaterol (see *Warnings and Special Precautions*).

Observed interactions to be considered

Metabolic and transporter based medicine interaction

Data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that a 2-fold AUC increase reflects the impact of maximal combined inhibition.

Interactions linked to glycopyrronium

Anticipated interactions resulting in concomitant use not being recommended

Anticholinergics

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

Observed interactions to be considered

Cimetidine or other inhibitors of organic cation transport

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 %.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been demonstrated.

Labour and delivery

Information related to indacaterol

ULTIBRO BREEZHALER may inhibit labour due to a relaxant effect on uterine smooth muscle.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety experience with ULTIBRO BREEZHALER was comprised of exposure of up to 15 months at the recommended therapeutic dose (110/50 µg).

The ULTIBRO BREEZHALER Phase III clinical development programme consisted of 6 key studies and enrolled over 6 000 patients with a clinical diagnosis of moderate to very severe COPD. Safety data from 5 of these studies with treatment durations of 12 weeks or longer were pooled from 1 805 patients exposed to ULTIBRO BREEZHALER 110/50 µg once-daily.

The frequency category for each adverse medicine reaction is based on the following convention (CIOMS III): very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports.

ULTIBRO BREEZHALER showed similar adverse medicine reactions as the individual components. As ULTIBRO BREEZHALER contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the components may be expected in the combination.

Adverse medicine reactions observed with ULTIBRO BREEZHALER in two placebo-controlled clinical trials

Adverse drug reactions	**Indacaterol/ glycopyrronium 110/50 µg once daily N=1106 Rate (95% CI)**	**Placebo N=748 Rate (95% CI)**	**Frequency category**
Infections and infestations			
Upper respiratory tract infection	16.96 (14.53, 19.74)	19.64 (16.67, 23.06)	Very common
Nasopharyngitis	9.03 (7.26, 11.20)	8.78 (6.77, 11.37)	Common
Urinary tract infection	2.86 (1.91, 4.29)	1.49 (0.80, 2.75)	Common
Sinusitis	1.8 (1.11, 2.93)	1.54 (0.82, 2.88)	Common
Rhinitis	1.86 (1.16, 2.99)	2.98 (1.16, 2.99)	Common
Immune system disorders			
Hypersensitivity	2.06 (1.31, 3.21)	1.90 (1.04, 3.47)	Common
Metabolism and nutrition disorders			
Hyperglycaemia and diabetes mellitus	1.65 (0.92, 2.95)	2.42 (1.46, 4.00)	Common
Psychiatric disorders			
Insomnia	0.81 (0.37, 1.76)	0.98 (0.44, 2.21)	Uncommon

Nervous system disorders			
Dizziness	1.74 (1.05, 2.88)	0.95 (0.42, 2.14)	Common
Headache	3.24 (2.28, 4.60)	2.66 (1.64, 4.29)	Common
Paraesthesia	0.09 (0.01, 0.64)	(0)	Rare
Eye disorders			
Glaucoma*	0.19 (0.05, 0.75)	(0)	Uncommon
Cardiac disorders			
Ischaemic heart disease	0.67 (0.32, 1.41)	0.78 (0.29, 2.12)	Uncommon
Atrial fibrillation	0.8 (0.33, 1.95)	0.24 (0.03, 1.68)	Uncommon
Tachycardia	0.39 (0.15, 1.04)	0.7 (0.29, 1.66)	Uncommon
Palpitations	0.73 (0.34, 1.56)	1.38 (0.68, 2.80)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Cough	6.84 (5.38, 8.68)	5.94 (4.30, 8.17)	Common
Oropharyngeal pain including throat irritation	2.95 (2.05, 4.23)	2.71 (1.70, 4.29)	Common
Epistaxis	0.28 (0.09, 0.85)	0.24 (0.03, 1.68)	Uncommon
Paradoxical bronchospasm	0.18 (0.05, 0.73)	0.51 (0.16, 1.64)	Uncommon
Gastrointestinal disorders			
Dyspepsia	2.29 (1.49, 3.51)	2.25 (1.32, 3.81)	Common

Dental caries	1.39 (0.79, 2.44)	0.97 (0.43, 2.19)	Common
Dry mouth	0.64 (0.31, 1.34)	0.45 (0.14, 1.39)	Uncommon
Gastroenteritis	0.28 (0.06, 1.18)	0.97 (0.43, 2.18)	Uncommon
Skin and subcutaneous tissue disorders			
Pruritus/rash	0.56 (0.25, 1.25)	0.91 (0.37, 2.24)	Uncommon
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	0.92 (0.47, 1.81)	1.3 (0.60, 2.78)	Uncommon
Muscle spasm	0.85 (0.41, 1.73)	0.44 (0.14, 1.37)	Uncommon
Pain in extremity	0.74 (0.37, 1.47)	0.14 (0.02, 0.98)	Uncommon
Myalgia	0.57 (0.25, 1.26)	0.53 (0.17, 1.70)	Uncommon
Renal and urinary disorders			
Bladder obstruction and urinary retention	1.03 (0.52, 2.03)	(0)	Common
General disorders and administration site conditions			
Pyrexia*	1.96 (1.26, 3.05)	1.47 (0.79, 2.72)	Common
Chest pain	1.85 (1.13, 3.02)	1.5 (0.77, 2.92)	Common
Peripheral oedema	0.65 (0.28, 1.48)	1.09 (0.51, 2.33)	Uncommon
Fatigue	0.83 (0.41, 1.68)	0.54 (0.20, 1.43)	Uncommon
Of the 1106 patients on ULTIBRO BREEZHALER, 946 (86%) were exposed for at least 26 weeks, and 447 (40%) were exposed for at least 52 weeks. Of the 748 patients on placebo, 588 (79%) were exposed for at least			

26 weeks, and 339 (45%) were exposed for at least 52 weeks.

*adverse drug reaction observed with the combination ULTIBRO BREEZHALER but not with the monotherapy components.

Post marketing:

Spontaneous reports:

The following adverse medicine reactions have been reported with ULTIBRO BREEZHALER in post-marketing experience.

Immune system disorders

Angioedema

Respiratory, thoracic and mediastinal disorders

Dysphonia

Additional information on individual components

Adverse medicine reactions are presented below for each component of ULTIBRO BREEZHALER. Additional adverse reactions previously reported with one of the individual components may occur with ULTIBRO BREEZHALER even if not observed in the pivotal clinical trials.

Indacaterol

Nasopharyngitis, headache, sinusitis, muscle spasm, rhinorrhea, peripheral oedema, myalgia, ischaemic heart disease, pruritus/rash, diabetes and hyperglycaemia, atrial fibrillation, hypersensitivity, paraesthesia, tachycardia, paradoxical bronchospasm.

Glycopyrronium

Dry mouth, gastroenteritis, insomnia, pain in extremity, rash, fatigue, asthenia, sinus congestion, rhinitis,

hyperglycaemia, hypoesthesia and atrial fibrillation.

Description of selected adverse drug reactions

The most common anticholinergic adverse event was dry mouth (0,6 % versus 0,3 % for placebo).

Serious adverse events, including hypersensitivity and ischaemic heart disease, have been reported as adverse medicine reactions for indacaterol administered as monotherapy. The reported frequencies for ULTIBRO BREEZHALER for hypersensitivity and ischaemic heart disease were 0,1 % versus 0,0 % for placebo and 0,1 % versus 0,3 % for placebo, respectively**.**

Special populations

In elderly patients above 75 years of age the frequencies of urinary tract infection and headache were higher on ULTIBRO BREEZHALER than on placebo, with 3,5 versus 2,8 %, respectively.

Reporting of suspected adverse reactions

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

4.9 Overdose

Treatment should be supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION:

A10.2.1 Bronchodilators (inhalants)

5.1 Pharmacodynamic properties

ULTIBRO BREEZHALER contains indacaterol and glycopyrronium bromide which have differing modes of action.

Indacaterol

Indacaterol is a long-acting $beta_2$-adrenergic agonist which when inhaled causes relaxation of smooth muscles.

Glycopyrronium bromide

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

5.2 Pharmacokinetic properties

Absorption

Following inhalation of ULTIBRO BREEZHALER, the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.

Absolute bioavailability of indacaterol after ULTIBRO BREEZHALER 110/50 microgram inhalation ranged from 47 % to 66 % whereas that of glycopyrronium was about 40 %**.**

Indacaterol

The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses. Systemic exposure to indacaterol increased with increasing dose (150 microgram to 600 microgram) in a dose proportional manner. Systemic exposure results from a composite of pulmonary and intestinal absorption.

Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-h dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2,9 to 3,8 for once-daily inhaled doses between 75 microgram and 600 microgram.

Glycopyrronium

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

About 90 % of systemic exposure following inhalation is due to lung absorption and 10 % is due to gastrointestinal absorption. The absolute bioavailability of orally administered glycopyrronium was estimated to be about 5 % .

Following repeated once-daily inhalation in patients with COPD, PK steady-state of glycopyrronium was reached within one week of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium for a 50 microgram once-daily dosing regimen were 166 pg/mL and 8 pg/mL, respectively. With once-daily doses of 100 and 200 microgram, steady-state exposure to glycopyrronium (AUC over the dosing interval) was about 1,4 -to 1,7-fold higher than after the first dose. Urinary excretion data at steady-state compared to the first dose suggest that systemic accumulation is independent of dose in the dose range of 25 to 200 microgram.

Metabolism

Indacaterol

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one third of total indacaterol-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. A phenolic O-glucuronide of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolised indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

Glycopyrronium

Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9) were seen.

In vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. The hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family.

It is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide by pre-systemic hydrolysis and/or via first pass metabolism. Only minimal amounts of M9 were found in the urine (i.e. ≤ 0,5 % of dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3 % of the dose.

In vitro inhibition studies demonstrated that glycopyrronium bromide 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 any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2**.**

Elimination

Indacaterol

The amount of indacaterol excreted unchanged *via* urine was generally lower than
2 % of the dose. Renal clearance of indacaterol was, on average, between 0,46 and 1,20 L/h. The serum clearance was indacaterol of 18,8 to 23,3 L/h**.**

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45,5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 56 hours which is consistent with the observed time to steady state of approximately 12 to 15 days.

Glycopyrronium

After I.V. administration of [^{3}H]-labelled glycopyrronium bromide to humans, the mean urinary excretion of radioactivity in 48 h amounted to 85 % of the dose. A further 5 % of the dose was found in the bile. Thus, mass balance was almost complete.

Renal elimination of parent substance accounts for about 60 to 70 % of total clearance of systemically available glycopyrronium whereas non-renal clearance processes account for about 30 to 40 %. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 50 and 200 microgram glycopyrronium by

healthy volunteers and patients with COPD mean renal clearance of glycopyrronium was in the range of 17,4 and 24,4 L/h. Active tubular secretion contributes to the renal elimination of glycopyrronium. Up to 20 % of the dose was found in urine as parent substance.

Glycopyrronium plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 57 hours) than after intravenous (6,2 hours) and oral (2,8 hours) administration. The elimination pattern suggests a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

Linearity/non-linearity

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

Patients with hepatic impairment

Based on the clinical PK characteristics of its monotherapy components, ULTIBRO BREEZHALER can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment**.**

Patients with renal impairment

Based on the clinical PK characteristics of its monotherapy components, ULTIBRO 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, ULTIBRO BREEZHALER is not recommended for use due to lack of data (see Warnings and Special precautions).

6 PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS:

Capsule fill: Lactose monohydrate, magnesium stearate.

Capsule shell components: Hypromellose, carrageenan, potassium chloride, FD&C Yellow5/Tartrazine.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store at or below 25 ºC and protect from moisture.

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

Keep out of reach of children.

6.5 Nature and contents of container

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

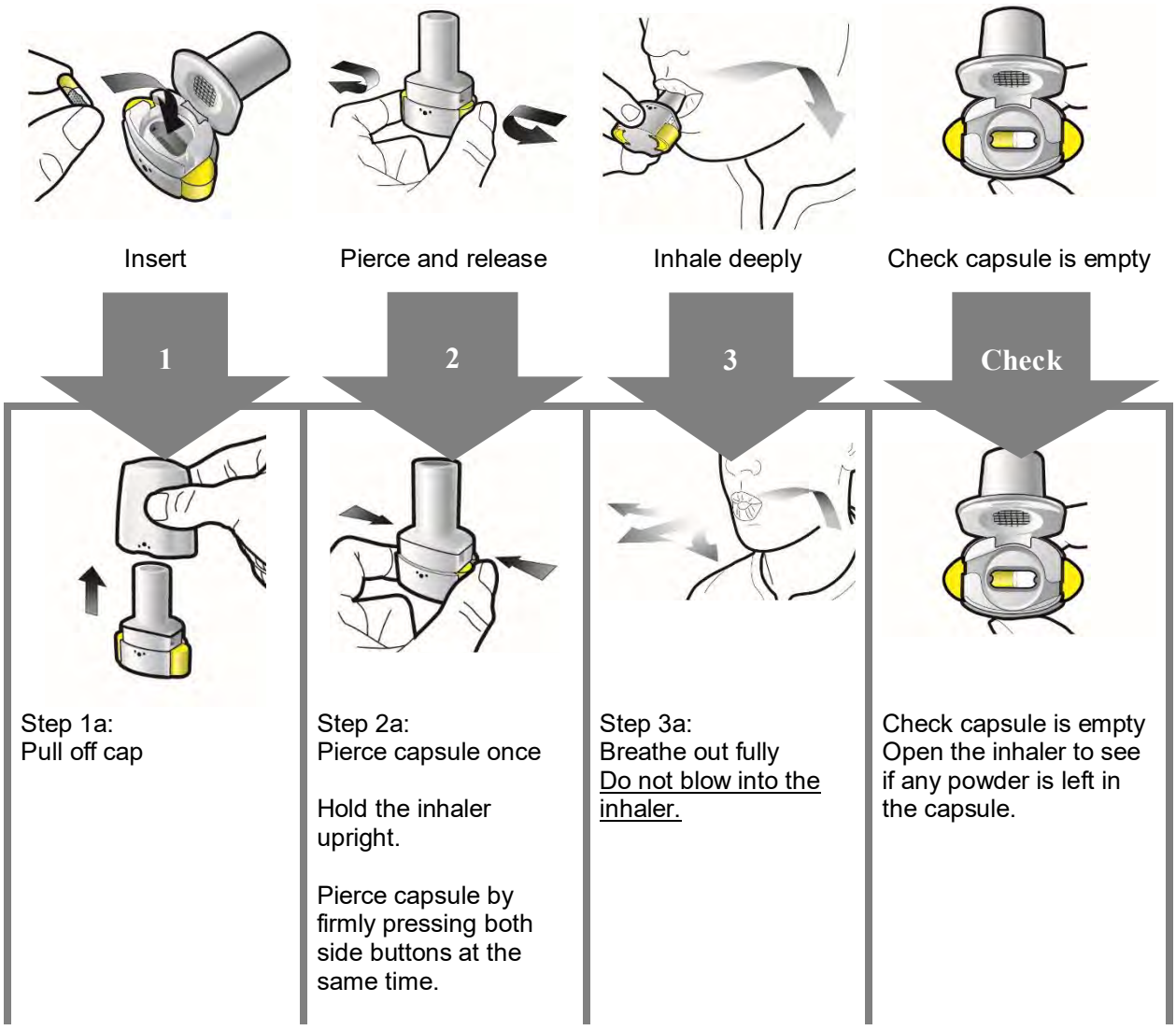
Each blister strip containing 6 or 10 capsules per blister is enclosed in a cardboard carton with 1 inhaler device.

The inhaler device is a plastic device comprising white cap and white body with yellow translucent push buttons.

Pack sizes: 30 capsules.

6.6 Special precautions for disposal

When prescribing ULTIBRO BREEZHALER patients should be instructed on correct use of the inhaler.



Step 1b:
Open inhaler

Step 1c:
Remove capsule

Separate one of the blisters from the blister card.

Peel open the blister and remove the capsule.

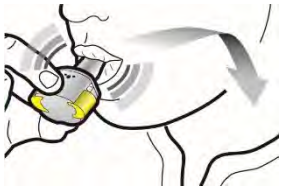
<u>Do not push the capsule through the foil.</u>

<u>Do not swallow the capsule.</u>

You should hear a noise as the capsule is pierced.

<u>Only pierce the capsule once.</u>

Step 2b:
Release side buttons



Step 3b:
Inhale medicine deeply

Hold the inhaler as shown in the picture.

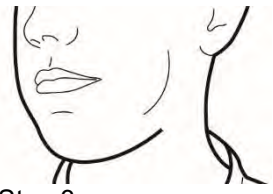
Place the mouthpiece in your mouth and close your lips firmly around it.

<u>Do not press the side buttons</u>.

Breathe in quickly and as deeply as you can.

During inhalation you will hear a whirring noise.

You may taste the medicine as you inhale.



Step 3c:
Hold breath

Hold your breath for up to 5 seconds.

If there is powder left in the capsule:

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

Powder remaining | Empty

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.

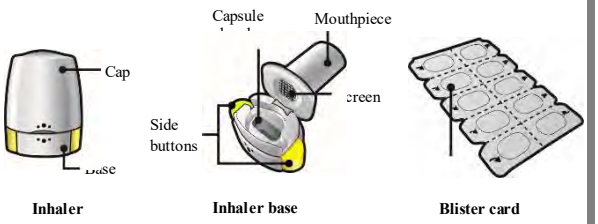
Step 1e:
Close inhaler

Important Information

- ULTIBRO 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 ULTIBRO Breezhaler capsules with any other inhaler.
- Do not use the ULTIBRO 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 ULTIBRO Breezhaler Inhaler pack contains:

- One ULTIBRO Breezhaler inhaler
- One or more blister cards, each containing either 6 or 10 ULTIBRO 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 South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View

Johannesburg

2090

8 MARKETING AUTHORISATION NUMBER(S)

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