NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ULTIBRO® BREEZHALER® 110/50 micrograms, powder filled inhalation capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 143 micrograms indacaterol maleate equivalent to 110 micrograms indacaterol and 63 micrograms glycopyrronium bromide (glycopyrrolate) 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.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Transparent yellow cap and natural transparent body capsules containing a white to practically white powder, with the product code IGP110.50 printed in blue under two blue bars on the body and the company logo (⏻) printed in black on the cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ULTIBRO BREEZHALER 110/50 is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD), and for the reduction of exacerbations of COPD in patients with a history of exacerbations.

4.2 Dose and method of administration

Dosage

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

Special populations

Elderly population

ULTIBRO BREEZHALER 110/50 can be used at the recommended dose in elderly patients 75 years of age and older.

Renal impairment

ULTIBRO BREEZHALER 110/50 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 110/50 should be used only if the expected benefit outweighs the potential risk (see section 4.4).

Hepatic impairment

ULTIBRO BREEZHALER 110/50 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.

Paediatric population

ULTIBRO BREEZHALER 110/50 should not be used in patients under 18 years of age, COPD is an indication of adults only. The safety and efficacy of Ultibro Breezhaler in children have not been established.

Method of administration

ULTIBRO BREEZHALER 110/50 capsules must be administered only by the oral inhalation route and only using the ULTIBRO BREEZHALER 110/50 inhaler. ULTIBRO BREEZHALER 110/50 capsules must not be swallowed (see section 4.9).

ULTIBRO BREEZHALER 110/50 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. Patients should be instructed not to take more than one dose in a day.

When prescribing ULTIBRO BREEZHALER 110/50 patients should be instructed on correct use of the inhaler. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it.

For instructions on administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
ULTIBRO 110/50 capsules contain lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

ULTIBRO BREEZHALER 110/50 should not be administered concomitantly with products containing other long-acting beta-adrenergic agonists or long-acting muscarinic antagonists, drug classes to which the components of ULTIBRO BREEZHALER 110/50 belong (see section 4.5).

Asthma and mixed airways disease
ULTIBRO BREEZHALER 110/50 should not be used for the treatment of asthma due to the absence of data in this indication.

Indacaterol, one of the active ingredients of ULTIBRO BREEZHALER 110/50, belongs to the class of long-acting beta$_2$- agonists. Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

A differential diagnosis should be made to exclude asthma or mixed airways disease before initiating ULTIBRO BREEZHALER 110/50. See section 5.2 for clinical experience to date.

Not for acute use
ULTIBRO BREEZHALER 110/50 is not indicated for the treatment of acute episodes of bronchospasm.

Hypersensitivity
Immediate hypersensitivity reactions have been reported after administration of indacaterol or glycopyrronium, which are components of ULTIBRO BREEZHALER 110/50. If signs suggesting allergic reactions occur, in particular, angioedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, ULTIBRO BREEZHALER 110/50 should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm
As with other inhalation therapy, administration of ULTIBRO BREEZHALER 110/50 may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ULTIBRO BREEZHALER 110/50 should be discontinued immediately and alternative therapy instituted.

Anticholinergic effect to glycopyrronium
Like other anticholinergic containing drugs, ULTIBRO BREEZHALER 110/50 should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Patients should be advised about signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using ULTIBRO BREEZHALER 110/50 and to contact their doctor immediately should any of these signs or symptoms develop.

Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a doctor immediately should any of these signs or symptoms develop.

Patients with severe renal impairment
For patients with severe renal impairment (estimated glomerular filtration rate below 30 mL/min/1.73 m2) including those with end-stage renal disease requiring dialysis, ULTIBRO BREEZHALER 110/50 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 drug reactions.

Systemic effects of beta-agonists
Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of ULTIBRO BREEZHALER 110/50 at the recommended dose, as with other compounds containing a beta$_2$-adrenergic agonist, ULTIBRO BREEZHALER 110/50 should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

As with other drugs containing an inhaled beta$_2$-adrenergic agonist, ULTIBRO BREEZHALER 110/50 should not be used more often or at higher doses than recommended.

Cardiovascular effects
ULTIBRO BREEZHALER 110/50 should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension).

Beta$_2$-adrenergic agonists may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur with this medicinal product, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiographic (ECG) changes, such as flattening of the T wave, prolongation of QT interval and ST segment depression, although the clinical significance of these observations is unknown. Therefore, long-acting beta$_2$-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 treated with medicinal products affecting the QT interval.

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) were excluded from the clinical trials, and therefore there is no experience in these patient groups. Ultibro Breezhaler should be used with caution in these patient groups.

Hypokalaemia with beta-agonists
Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment (see section 4.5) which may increase the susceptibility to cardiac arrhythmias.

Clinically relevant effects of hypokalemia have not been observed in clinical studies of ULTIBRO BREEZHALER 110/50 at the recommended therapeutic dose (see section 5.1).

Hyperglycaemia with beta-agonists
Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with ULTIBRO BREEZHALER 110/50 plasma glucose should be monitored more closely in diabetic patients. During long-term clinical studies ([ENLIGHTEN] and [RADIATE]), more patients on ULTIBRO BREEZHALER 110/50 experienced clinically notable changes in blood glucose (4.9%) than on placebo (2.7%). ULTIBRO BREEZHALER 110/50 has not been investigated in patients for whom diabetes mellitus is not well controlled.

4.5 Interaction with other medicines and other forms of interaction

Interactions linked to ULTIBRO BREEZHALER 110/50
Following single doses of glycopyrronium bromide (glycopyrrolate) and indacaterol alone and in combination there were small yet significant increases in the exposure to both drugs following combination treatment compared with the monotherapies. Under steady state conditions of both drugs, although indacaterol exposure was unaffected by co-administration there was a small but significant increase in glycopyrronium Cmax when given in combination. Overall these differences are unlikely to be clinically significant. No specific drug-drug interaction studies were conducted with ULTIBRO BREEZHALER 110/50. Information on the potential for interactions for

ULTIBRO BREEZHALER 110/50 is based on the potential for each of its two monotherapy components.

No studies have examined the PD interaction between ULTIBRO BREEZHALER 110/50 and drugs commonly used in the treatment of COPD or frequently observed co-morbidities such as cardiovascular disease, these include salbutamol, ipratropium bromide and beta-blockers; therefore, caution should be taken when co-administering ULTIBRO BREEZHALER 110/50 with drugs used for the treatment of COPD, asthma, hypertension or cardiac disease.

Interactions linked to indacaterol
In vitro investigations have indicated that indacaterol has negligible potential to cause metabolic interactions with medications at the systemic exposure levels achieved in clinical practice (see section 5.2).

Beta-adrenergic blockers
Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-adrenergic agonists.
Therefore ULTIBRO BREEZHALER 110/50 should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Drugs known to prolong QTc interval
ULTIBRO BREEZHALER 110/50, as other $beta_2$-adrenergic agonist containing drugs, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia (see section 4.4).

Sympathomimetic agents
Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of indacaterol (see section 4.4).

Hypokalemic treatment
Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists (see section 4.4).

Metabolic and transporter based drug interaction
Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin verapamil and ritonavir). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to two-fold increase in AUC and 1.5-fold increase in Cmax. Co-administration of erythromycin with indacaterol resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and Cmax, respectively. Concomitant treatment with ritonavir, another dual inhibitor of CYP3A4 and P-gp, resulted in a 1.6- to 1.8-fold increase in AUC whereas Cmax was unaffected. Taken together, the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. The magnitude of exposure increases due to drug interactions does not raise any safety concerns

given the safety experience of treatment with indacaterol in clinical trials of up to one year at doses of 600 microgram.

Interactions linked to glycopyrronium
In vitro studies showed that glycopyrronium is not likely to inhibit or induce the metabolism of other drugs, nor processes involving drug transporters. Metabolism in which multiple enzymes are involved, plays a secondary role in the elimination of glycopyrronium (see section 5.2). Inhibition or induction of metabolism of glycopyrronium is unlikely to result in a relevant change of systemic exposure to the drug.

Anticholinergics
The co-administration of ULTIBRO BREEZHALER 110/50 with inhaled anticholinergic-containing drugs has not been studied and is therefore, like for other anticholinergic-containing drugs, not recommended.

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%. 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 the organic cation transport.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category B3)
There are no data from the use of ULTIBRO BREEZHALER 110/50 in pregnant women available. Likewise there are no data from the use of either indacaterol or glycopyrronium in pregnant women.

Like other beta$_2$-adrenergic agonist containing drugs, ULTIBRO BREEZHALER 110/50 may inhibit labor due to a relaxant effect on uterine smooth muscle.

No adverse embryofetal effects were seen following inhalational administration of glycopyrronium and indacaterol in combination in rats. Plasma AUC values at the highest dose tested were 79 and 125 times the human AUC for indacaterol and glycopyrronium, respectively.

Information related to indacaterol
Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration at doses up to 1 and 3 mg/kg/day in the respective species. An increase in the incidence of a rib skeletal variation and retarded ossification were observed in the rabbit, possibly secondary to maternal toxicity. The plasma AUC at the no effect level in animals was at least 170 times the AUC in humans at the maximum recommended dose of indacaterol provided by ULTIBRO BREEZHALER 110/50.

Information related to glycopyrronium
Glycopyrronium bromide (glycopyrrolate) was not teratogenic in rats or rabbits following inhalational administration at doses up to 3.05 and 3.5 mg/kg/day in the respective species (yielding plasma AUC values 730-times and 250-times higher than in patients at the maximum recommended human dose). Glycopyrronium bromide (glycopyrrolate) and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of

0.006 mg/kg glycopyrronium bromide (glycopyrrolate), umbilical plasma concentrations were low.

The potential risk for humans is unknown. Therefore as there is no adequate experience in pregnant women, ULTIBRO BREEZHALER should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Breastfeeding
It is not known whether indacaterol and/or glycopyrronium passes into human breast milk. Indacaterol and glycopyrronium (including their metabolites) have been detected in the milk of lactating rats. Reduced body weight gain was observed in pups of rats treated with indacaterol or glycopyrronium, while impaired learning and decreased fertility were observed in pups of rats treated with indacaterol during pregnancy and lactation. Therefore the use of ULTIBRO BREEZHALER 110/50 by breastfeeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Fertility
No studies on the effect on fertility have been conducted with the indacaterol/ glycopyrronium combination.

Information related to indacaterol
No adverse effects on fertility were observed in male and female rats given indacaterol by subcutaneous injection at doses up to 2 mg/kg/day (yielding greater than 450-times [males] and 340-times [females] the serum AUC in humans at the maximum recommended dose of 110 µg/day provided by ULTIBRO BREEZHALER 110/50).

Information related to glycopyrronium
Male and female fertility were unaffected in rats given glycopyrronium bromide (glycopyrrolate) by subcutaneous administration at doses up to 1.5 mg/kg/day (yielding plasma AUC levels approximately 900-times [males] and 500- times [females] that of humans at the maximum recommended clinical dose of 50 µg). Slight inhibition of ovulation (decreased corpora lutea) and increased pre-implantation loss were evident at this highest dose, but not at 0.5 mg/kg/day (relative exposure based on AUC, 162).

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines. However, the occurrence of dizziness may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The presentation of the safety profile of ULTIBRO BREEZHALER 110/50 is based on the experience with ULTIBRO BREEZHALER 110/50 and the individual monotherapy components.

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

The ULTIBRO BREEZHALER 110/50 Phase III clinical development program consisted of 11 key studies and enrolled over 10000 patients with a clinical diagnosis of moderate to very severe

COPD. Safety data from 9 of these studies with treatment durations of 4 weeks or longer were pooled from 4352 patients exposed to ULTIBRO BREEZHALER 110/50 microgram once-daily.

The safety profile was characterised by typical anticholinergic and beta-adrenergic symptoms related to the individual monotherapy components of the combination. Other most common adverse drug reactions related to the drug product (≥3% and greater than placebo) were headache, cough and nasopharyngitis.

At the recommended dose, the adverse drug reaction profile of ULTIBRO BREEZHALER110/50 in patients with COPD showed clinically insignificant systemic effects of beta$_2$-adrenergic stimulation. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a lower rate than with placebo. Relevant prolongations of QTcF were not detectable in comparison to placebo. The frequency of notable QTcF intervals [i.e., >450 ms] and reports of hypokalemia were similar to placebo.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions (ADR) are listed by MedDRA system organ class (Table 2). The frequency of adverse drug reactions was based on a pool of 3 Phase III placebo-controlled trials of 6 and 12 months in duration. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000, <1/1,000); and very rare (<1/10,000).

ULTIBRO BREEZHALER110/50 showed similar adverse drug reactions as the individual monotherapy components. As ULTIBRO BREEZHALER 110/50 contains indacaterol and glycopyrronium, the type and severity of adverse reactions associated with each of the monotherapy components may be expected in the combination.

Table 2 Kaplan-Meier cumulative incidence (%) of the adverse drug reactions at week 52 (Placebo-controlled COPD Pool)

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

Adverse drug reactions	Indacaterol/ glycopyrronium 110/50 µg once daily n=1106 Rate (95% CI)	Placebo n=748 Rate (95% CI)	Frequency category
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 incl 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 disorder			
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 110/50 but not with the monotherapy components.

Study 2307

For the 12-month trial A2307 comparing ULTIBRO BREEZHALER 110/50 (n=226) and placebo (n=113), the most commonly reported AE was COPD (ULTIBRO BREEZHALER 110/50 28.0% vs. placebo 25.7%). Cough, lower respiratory tract infections, pyrexia and pneumonia were reported

for a slightly higher percentage of patients in the ULTIBRO BREEZHALER 110/50 group compared with placebo.

Five deaths were reported in this study, four in the Ultibro Breezhaler 110/50 group (1.8%) and 1 in the placebo group (0.9%). In the Ultibro Breezhaler 110/50 group 1 sudden death was adjudicated to cardiovascular cause. Three deaths were adjudicated to respiratory cause (COPD exacerbations, including 1 with pneumonia). The cause of the 1 death observed in the placebo group was accidental.

A higher proportion of patients in the ULTIBRO BREEZHALER 110/50 group had severe COPD (31.1%) compared to placebo (18.6%) at baseline. Inhaled corticosteroid use was also higher in the ULTIBRO BREEZHALER 110/50 group compared with placebo (45.8% vs. 38.9%) at baseline, whereas more patients had a history of cardiovascular disease in the placebo group than in the ULTIBRO BREEZHALER 110/50 group.

Post-marketing experience: Adverse drug reactions from spontaneous reports and literature cases
The following adverse drug reactions have been reported with ULTIBRO BREEZHALER 110/50 in post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

Immune system disorders:
Angioedema
Respiratory, thoracic and mediastinal disorders:
Dysphonia

Description of selected adverse drug reactions
The most common anticholinergic adverse event was dry mouth (0.64% versus 0.45% for placebo); however, this adverse event was reported at a lower frequency with ULTIBRO BREEZHALER 110/50 than with glycopyrronium monotherapy. The majority of the reports of dry mouth were suspected to be drug related and of mild degree, none was severe. Cough was common, but usually of mild intensity.

Some serious adverse events, including hypersensitivity and ischaemic heart disease, have been reported as ADRs for indacaterol administered as monotherapy. The reported frequencies for ULTIBRO BREEZHALER 110/50 for hypersensitivity and ischaemic heart disease were 2.06% versus 1.9% for placebo and 0.67% versus 0.78% for placebo, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Information related to ULTIBRO BREEZHALER 110/50
In a single dose study in healthy volunteers the 4-fold of the therapeutic dose of ULTIBRO BREEZHALER 110/50 (four dose steps of 110/50 microgram separated by one hour, each) was well tolerated with no relevant effects on heart rate, QTc-interval, serum potassium or blood glucose.

In COPD patients, doses of up to 600/100 microgram ULTIBRO BREEZHALER 110/50 were inhaled over two weeks and there were no relevant effects on heart rate, QTc-interval, blood glucose or serum potassium. There was an increase in ventricular ectopies after 14 days of dosing with 300/100 and 600/100 microgram ULTIBRO BREEZHALER 110/50, but low prevalence and small patient numbers (N=49 and N=51 for 600/100 microgram and 300/100 microgram ULTIBRO BREEZHALER 110/50, respectively) did preclude accurate analysis. In a total of four patients non-sustained ventricular tachycardia was recorded with the longest episode recorded being 9 beats (4 seconds).

An overdose could lead to exaggerated effects typical of $beta_2$-adrenergic stimulants, i.e. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia, and hyperglycemia or could induce anticholinergic effects, i.e. increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding. Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised. Use of cardioselective beta blockers may be considered for treating $beta_2$-adrenergic effects, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm.

Information related to indacaterol
In COPD patients single doses of 3000 microgram were associated with a moderate increase in pulse rate, systolic blood pressure increase and QTc interval.

Information related to glycopyrronium
In COPD patients, repeated orally inhaled administration of glycopyrronium at total doses of 100 and 200 microgram once-daily for 28 days were well tolerated.
Acute intoxication by inadvertent oral ingestion of glycopyrronium capsules is unlikely due to the low oral bioavailability (about 5%).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergics in combination with anticholinergics, ATC code: R03AL04.

Mechanism of action
ULTIBRO BREEZHALER 110/50

When indacaterol and glycopyrronium are administered together in ULTIBRO BREEZHALER 110/50, they are expected to provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve smooth muscle relaxation. Due to the differential density of beta$_2$-adrenoceptors and M3-receptors in central versus smaller airways, beta$_2$-agonists should be more effective in relaxing small airways whilst an anti-cholinergic compound may be more effective in large airways. Thus for optimal bronchodilation in all regions of the human lung, a combination of a beta$_2$-adrenergic agonist and a muscarinic antagonist may be beneficial.

Indacaterol

Indacaterol is an 'ultra' long-acting beta$_2$-adrenergic agonist for once-daily administration. The pharmacological effects of beta$_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic monophosphate). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol has more than 24-fold greater agonist activity at beta$_2$-receptors compared to beta-receptors and 20-fold greater agonist activity compared to beta$_3$-receptors. This selectivity profile is similar to formoterol.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human beta$_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although beta$_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-adrenergic receptors are the predominant receptors in the human heart, there are also beta$_2$-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta$_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta$_2$-adrenergic agonists may have cardiac effects.

Glycopyrronium

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic) 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.

Of the five known muscarinic receptor subtypes (M1-5), only subtypes M1-3 have a defined physiological function in the human lung. Glycopyrronium bromide (glycopyrrolate) is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M3 and M1 receptors over the human M2 receptor in competition 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 drug concentrations in the lungs as reflected by the prolonged terminal elimination half-life of glycopyrronium after inhalation via the glycopyrronium inhaler in contrast to the half-life after i.v. administration (see section 5.2). Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide (glycopyrrolate) provides further evidence for this.

Pharmacodynamic effects

Primary Pharmacodynamic Effects
The combination of indacaterol and glycopyrronium in ULTIBRO BREEZHALER 110/50 showed a rapid onset of action within 5 minutes after dosing (see section 5.1, Table 1-2). The effect remains constant over the whole 24 h dosing interval (see section 5.1, Figures 1-1 and 1-2).

The mean bronchodilator effect derived from serial FEV1 measurements over 24 h was 0.32 L after 26 weeks of treatment when compared to placebo. The effect was significantly greater for ULTIBRO BREEZHALER 110/50, when compared to indacaterol, glycopyrronium or tiotropium alone (difference 0.11 L, for each comparison), (serial spirometry subset).

There was no evidence for tachyphylaxis to the effect of ULTIBRO BREEZHALER 110/50 over time when compared to placebo or its monotherapy components.

Secondary Pharmacodynamic Effects
The systemic side effects of inhaled beta$_2$-adrenergic agonists and inhaled muscarinic receptor antagonists are the result of activation of systemic beta$_2$-adrenergic receptors and blockade of muscarinic receptors after systemic absorption of the drugs. The side effect profile of ULTIBRO BREEZHALER 110/50 was explored in healthy subjects) and in COPD patients.

Effects on heart rate
Heart rate effects in healthy volunteers were investigated after a single dose of ULTIBRO BREEZHALER 440/200 microgram administered in four dose steps separated by one hour and compared to the effects of placebo, 600 microgram indacaterol, 200 microgram glycopyrronium and 200 microgram salmeterol.

The largest time matched heart rate increase for ULTIBRO BREEZHALER 110/50 compared to placebo was +5.69 bpm, the largest decrease was -2.51 bpm. Overall the effect on heart rate over time did not show a consistent PD-effect of ULTIBRO BREEZHALER 110/50.

There were no significant effects when ULTIBRO BREEZHALER 110/50 was compared with indacaterol and glycopyrronium alone. Heart rate in COPD patients at supratherapeutic dose levels was investigated in ULTIBRO BREEZHALER 110/50 up to doses of 150/100, 300/100 and 600/100 microgram. There were no relevant effects of ULTIBRO BREEZHALER 110/50 on mean heart rate over 24 h and heart rate assessed after 30 min, 4 h and 24 h.

QT-interval
A thorough QT (TQT) -study in healthy volunteers with doses of inhaled indacaterol up to 600 micrograms did not demonstrate a clinically relevant effect on the QT-interval. Also for glycopyrronium, no QT-prolongation has been observed in a TQT study after an inhaled dose of 400 microgram.

The effects of ULTIBRO BREEZHALER 110/50 on QTc-interval were investigated in healthy volunteers after inhalation of ULTIBRO BREEZHALER 440/200 microgram in four dose steps separated by one hour. The largest time matched difference versus placebo was 4.62 ms (90% CI 0.40, 8.85 ms), the largest time matched decrease was -2.71 ms (90% CI -6.97, 1.54 ms), indicating that ULTIBRO BREEZHALER 110/50 had no relevant impact on the QT-interval as was expected by the properties of its components.

In COPD patients, doses up to 600/100 microgram ULTIBRO BREEZHALER also had no apparent influence on the QTc-interval in repeated ECG assessments executed between 15 min and 24 h after dosing. A slightly higher proportion of patients had QTc-prolongations above 450 ms at the ULTIBRO BREEZHALER 600/100 microgram group. The number of notable QTcF changes versus baseline (>30 ms) was similar across all active treatment groups (ULTIBRO BREEZHALER 600/100 microgram, 300/100 microgram, 150/100 microgram and indacaterol 300 microgram), but was lower with placebo.

Serum potassium and blood glucose
In healthy volunteers, after administration of ULTIBRO BREEZHALER 440/200 microgram, the effect on serum potassium was very small (maximal difference −0.14 mmol/L when compared to placebo). The maximal effect on blood glucose was 0.67 mmol/L. When ULTIBRO BREEZHALER 440/200 microgram was compared with 200 microgram salmeterol, the effect on serum potassium (maximum difference 0.21 mmol/L) and blood glucose was smaller (maximum difference 0.21 and 1.19 mmol/L, respectively).

Clinical efficacy and safety
The ULTIBRO BREEZHALER 110/50 Phase III clinical development program [IGNITE] included six studies in which over 8,000 patients were enrolled: one 26-week placebo- and active-controlled (indacaterol 150 microgram once daily, glycopyrronium 50 microgram once daily, open-label tiotropium 18 microgram once daily) study [SHINE]; one 26-week active-controlled (fluticasone/salmeterol 500/50 microgram twice daily) study [ILLUMINATE]; a 64-week active controlled (glycopyrronium 50 microgram once daily, open-label tiotropium 18 microgram once daily) study [SPARK]; a 52-week placebo-controlled study [ENLIGHTEN] ; a 3-week placebo- and active-controlled (tiotropium once daily) exercise tolerance study [BRIGHT]; and a 52-week active-controlled (fluticasone/salmeterol 500/50 microgram twice daily) study [FLAME].

These studies enrolled patients with a clinical diagnosis of moderate to very severe COPD, who were 40 years old or older, and had a smoking history of at least 10 pack years. Of these 4 studies, the [SHINE] and [ENLIGHTEN] studies had a post-bronchodilator FEV1 <80% and ≥30% of the predicted normal value and a post-bronchodilator FEV1/FVC ratio of less than 70%. The 26-week active-controlled study, [ILLUMINATE], enrolled patients with a post-bronchodilator FEV1 of <80% and ≥40% of the predicted normal value. In comparison, the 64-week [SPARK] study enrolled patients with severe to very severe COPD, with a history of ≥1 moderate or severe COPD exacerbation in the previous year, and a post-bronchodilator FEV1 <50% of the predicted normal value. Patients with significant concomitant illnesses including Type 1 or uncontrolled Type 2 diabetes, significantly abnormal ECG (including QTc prolongation), narrow angle glaucoma, urinary retention, severe renal failure, patients requiring long-term oxygen therapy, patients with recent acute COPD exacerbations or URTI, patients with other significant pulmonary disease including asthma, patients with atopy or intermittent allergic rhinitis were excluded from the COPD trials. Patients with unstable ischemic heart disease, left ventricular failure (NYHA Class III & IV), history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation) were also excluded. The 52-week active-controlled study, [FLAME], enrolled moderate to very severe COPD patients with a history of ≥1 moderate or severe COPD exacerbation (19% had a history of ≥2 exacerbations) in the previous year, and a post-bronchodilator FEV1 of ≥25 and < 60% of the predicted normal value.

Effects on lung function
ULTIBRO BREEZHALER 110/50 administered at 110/50 microgram once daily showed clinically meaningful improvements in lung function (as measured by the forced expiratory volume in one second, FEV1), 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. Within the 26-week [SHINE] and 52-week [ENLIGHTEN] studies, there was no attenuation of the bronchodilator effect over time.

Trough FEV_1

In the [SHINE] study, ULTIBRO BREEZHALER 110/50 increased post-dose trough FEV1 by 200 mL compared to placebo at the 26-week primary endpoint (p<0.001) and showed significant increases compared to each monotherapy component treatment arm (indacaterol and glycopyrronium) as well as the tiotropium treatment arm (see Table 1-1).

Table 1-1 Post-dose trough FEV1 (least squares mean) at Day 1 and Week 26 (primary endpoint)

Treatment difference	Day 1	Week 26
ULTIBRO BREEZHALER 110/50 - placebo	190 mL (p<0.001)	200 mL (p<0.001)
ULTIBRO BREEZHALER 110/50 – indacaterol	80 mL (p<0.001)	70 mL (p<0.001)
ULTIBRO BREEZHALER 110/50 – glycopyrronium	80 mL (p<0.001)	90 mL (p<0.001)
ULTIBRO BREEZHALER 110/50 – tiotropium	80 mL (p<0.001)	80 mL (p<0.001)

The mean pre-dose FEV1 (average of the values taken at -45 and -15 min prior to the morning dose of study drug) was clinically meaningful and statistically significant in favor of ULTIBRO BREEZHALER 110/50 at Week 26 compared to fluticasone/salmeterol (100 mL, p<0.001) [ILLUMINATE], at Week 52 compared to placebo (189 mL, p<0.001) [ENLIGHTEN] and at all visits up to Week 64 compared to glycopyrronium (70 80 mL, p-value <0.001) and tiotropium (60-80 mL, p-value <0.001) [SPARK]. In the [FLAME] study, the mean pre-dose FEV1 was clinically meaningful and statistically significant in favor of ULTIBRO BREEZHALER 110/50 at all visits up to Week 52 compared to fluticasone/salmeterol (62-86 ml, p<0.001).

Peak FEV_1

ULTIBRO BREEZHALER 110/50 produced statistically significant improvement in peak FEV1 compared to placebo in the first 4 hours post-dose on Day 1 (210 mL, p<0.001), at Week 26 (330 mL, p<0.001), and compared to indacaterol (120 mL), glycopyrronium (130 mL), tiotropium (130 mL) at Week 26 (p<0.001 for all comparisons) [SHINE], and compared to fluticasone/salmeterol on Day 1 (70 mL, p<0.001) and Week 26 (150 mL, p<0.001) [ILLUMINATE].

FEV_1 AUC

ULTIBRO BREEZHALER 110/50 increased post-dose FEV1 AUC0-12 (primary endpoint) by 140 mL at 26 weeks (p<0.001) in the active-controlled [ILLUMINATE] study compared to fluticasone/salmeterol.

Onset of action

In the [SHINE and ILLUMINATE] studies, ULTIBRO BREEZHALER 110/50 demonstrated a statistically significant rapid onset of bronchodilator effect on Day 1 and at Week 26.

Table 1-2 Onset of action versus placebo, tiotropium and fluticasone/salmeterol at 5 and 30 minutes on Day 1 and Week 26

	Day 1	Week 26
versus placebo		
5 minutes	130 mL*	290 mL*
30 minutes	200 mL*	320 mL*
versus tiotropium		
5 minutes	70 mL*	120 mL*
30 minutes	90 mL*	140 mL*
versus fluticasone/salmeterol		
5 minutes	80 mL*	150 mL*
30 minutes	80 mL*	160 mL*

* $p < 0.001$ for all treatment comparisons

Serial spirometry subset

In the 26-week, placebo-controlled [SHINE] study, 12-hour serial spirometry was performed on Day 1 (Figure 1-1) and 24-hour serial spirometry at Week 26 (Figure 1-2) in a subset of 294 patients. Serial FEV1 values over 12 hours at Day 1 and trough FEV1 values at Day 2 are shown in Figure 12-1, and at Week 26 in Figure 12-2. Improvement of lung function was maintained for 24 hours after the first dose and consistently maintained over the 26-week treatment period with no evidence of tolerance.

Figure 1-1 24 hour profile of least squares means of FEV1 (L) at Day 1 (FAS, serial spirometry subset)

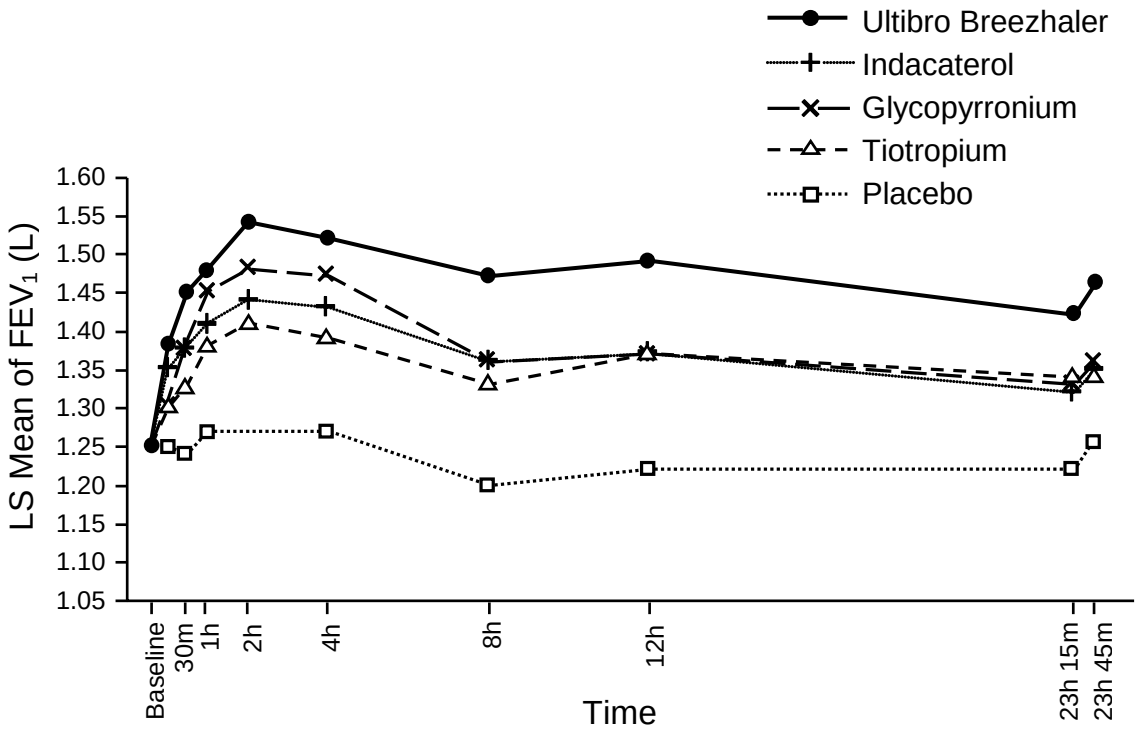
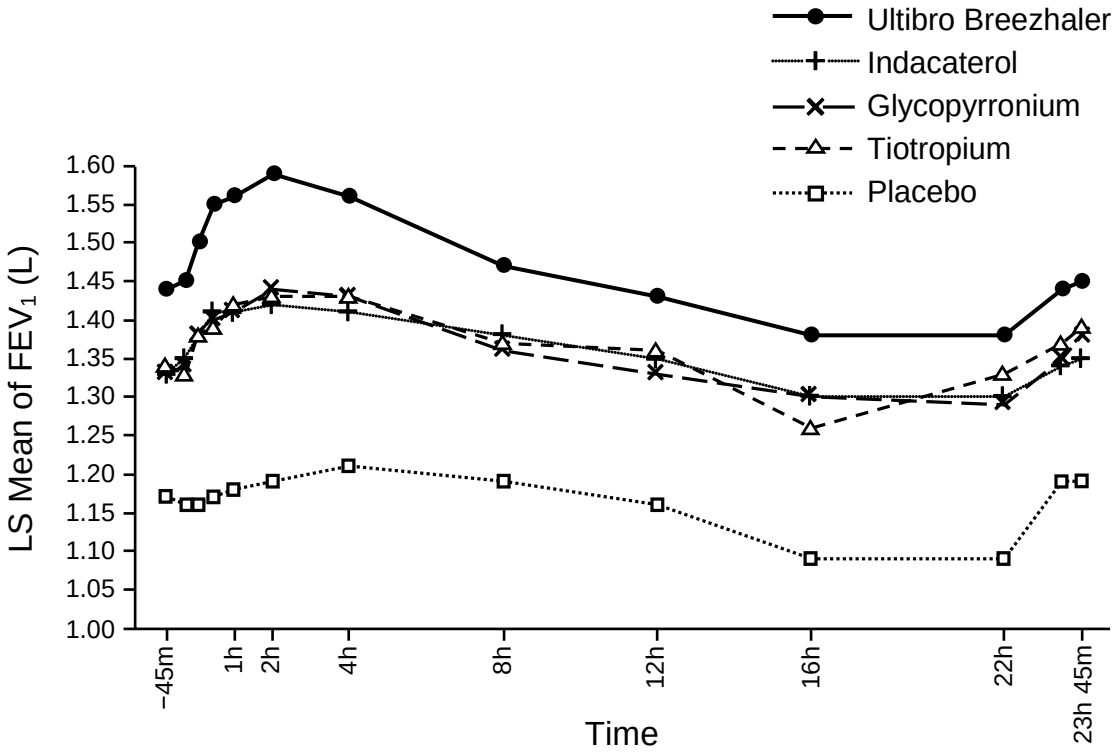


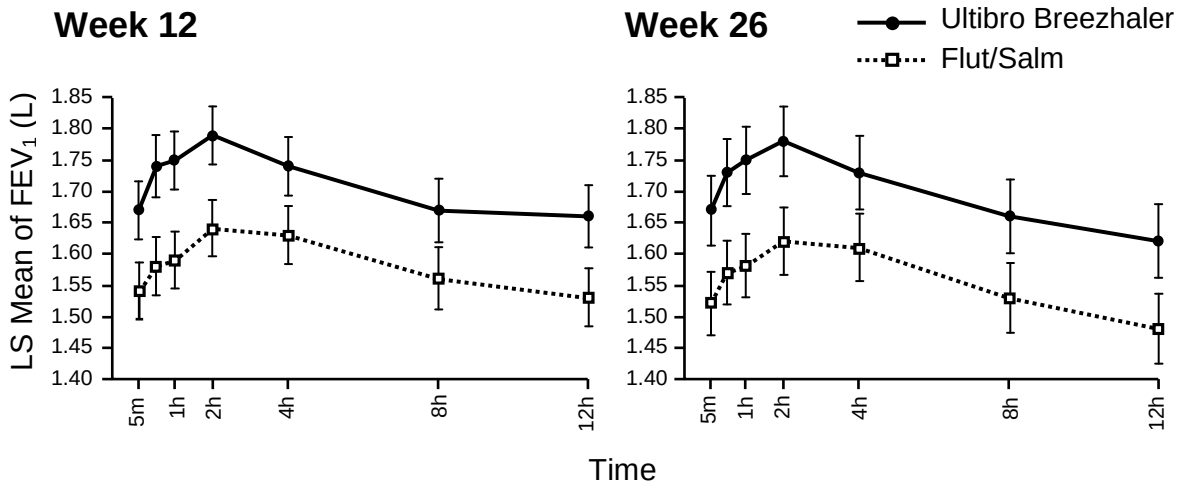
Figure 1-2 **23 h 45 min profile of least squares means of FEV1 (L) after 26 weeks of treatment (FAS, serial spirometry subset)**



In the [SHINE] serial spirometry subset, ULTIBRO BREEZHALER demonstrated a statistically significant improvement in FEV1 compared to placebo (400 mL, p<0.001) and tiotropium (160 mL, p<0.001) at 2 hours post-dose at Week 26.

ULTIBRO BREEZHALER 110/50 also had clinically meaningful and statistically significant improvements in FEV1 compared to fluticasone/salmeterol across all time points from 5 minutes post-dose up to 12 hours post-dose at both Week 12 (p<0.001) and Week 26 (p<0.001) [ILLUMINATE] (see Figure 1-3).

Figure 1-3 **Profile of LS means of FEV1 (L) from 5 min up to 12 h post-dose at Week 12 and Week 26 (Full analysis set)**

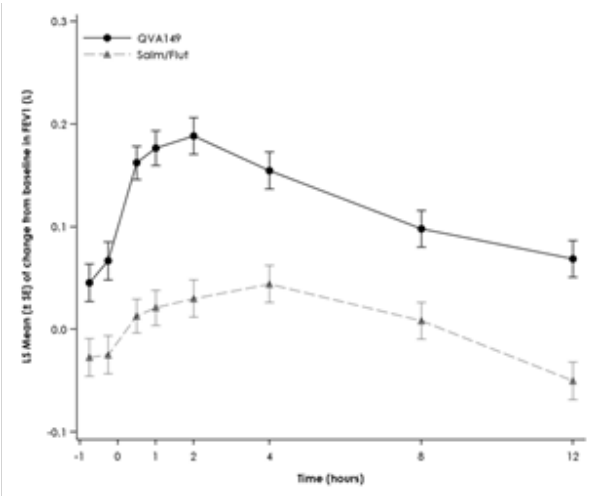


In the [ILLUMINATE] study, ULTIBRO BREEZHALER 110/50 demonstrated significant overall improvements in lung function compared with fluticasone/salmeterol, across all key subgroups, including age, gender, smoking history, disease severity, and reversibility.

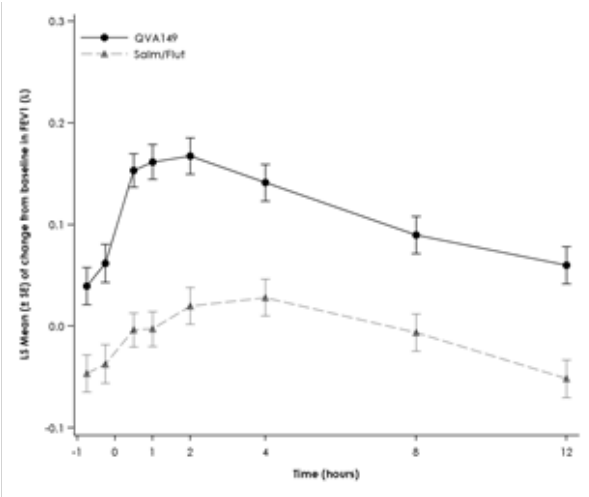
In the [FLAME] serial spirometry subset, ULTIBRO BREEZHALER 110/50 demonstrated clinically meaningful and statistically significant improvements in FEV1 AUC0-12h at 52 weeks of treatment. The ULTIBRO BREEZHALER 110/50 group was statistically superior to the fluticasone/salmeterol group from Day 1 onwards (all $p<0.05$).

Figure 1-4 Profile of least squares mean change from baseline in FEV_1 (L) -45 min to 12h at Week 12, Week 26, and Week 52 (Serial spirometry set)

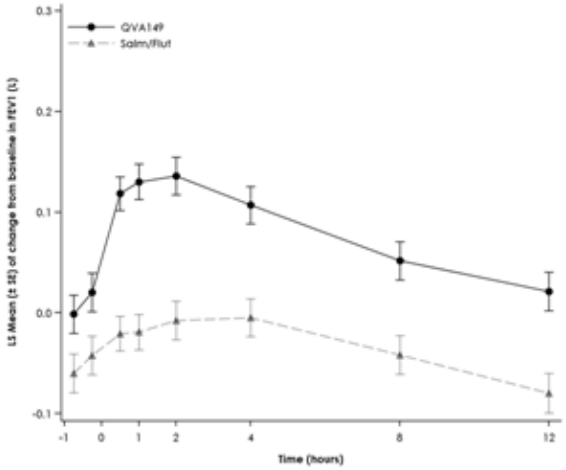
Week 12



Week 26



Week 52



QVA149 = Ultibro Breezhaler 110/50

Symptomatic benefit

Breathlessness

ULTIBRO BREEZHALER 110/50 significantly reduced breathlessness as evaluated by the Transitional Dyspnoea Index (TDI). ULTIBRO BREEZHALER 110/50 demonstrated a clinically meaningful and statistically significant improvement in the TDI focal score at Week 26 as compared to placebo (1.09, p<0.001), tiotropium (0.51, p=0.007) [SHINE], and fluticasone/salmeterol (0.76, p=0.003) [ILLUMINATE].

A significantly higher percentage of patients receiving ULTIBRO BREEZHALER 110/50 responded with a 1 point or greater improvement in the TDI focal score at Week 26 compared to placebo (68.1% and 57.5% respectively, p=0.004). A higher proportion of patients demonstrated clinically meaningful response at Week 26 on ULTIBRO BREEZHALER 110/50 as compared to tiotropium (68.1% ULTIBRO BREEZHALER vs. 59.2% tiotropium, p=0.016) [SHINE] and fluticasone/salmeterol (65.1% ULTIBRO BREEZHALER 110/50 vs. 55.5% fluticasone/salmeterol, p=0.088) [ILLUMINATE].

Health related quality of life

ULTIBRO BREEZHALER 110/50 once daily has also shown a statistically significant effect on health related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) at 26 weeks as indicated by a reduction in SGRQ total score compared to placebo (3.01, p=0.002) and tiotropium (-2.13, p=0.009) [SHINE], at 64 weeks compared to tiotropium (-2.69, p<0.001) [SPARK], and at 52 weeks compared to fluticasone/salmeterol (-1.3, p=0.003) [FLAME]. In addition, improvements of the domains of the SGRQ score "symptoms", "activity" and "impact of daily life" were all statistically significant versus tiotropium at Week 64 ("symptoms": -3.06, p=0.003, "activity": -3.14, p < 0.001, "impact of daily life": -2.24, p=0.008) [SPARK].

A higher percentage of patients receiving ULTIBRO BREEZHALER 110/50 responded with a clinically meaningful improvement in SGRQ score (defined as a decrease of at least 4 units from baseline) at Week 26 compared to placebo (63.7% and 56.6% respectively, p=0.088) and tiotropium (63.7% ULTIBRO BREEZHALER 110/50 vs. 56.4% tiotropium, p=0.047) [SHINE] , and at Week 64 compared to glycopyrronium and tiotropium (57.3% ULTIBRO BREEZHALER 110/50 vs. 51.8% glycopyrronium, p=0.055; vs. 50.8% tiotropium, p=0.051, respectively) [SPARK], and at Week 52 compared to fluticasone/salmeterol (49.2% ULTIBRO BREEZHALER 110/50 vs. 43.7% fluticasone/salmeterol, OR: 1.30, p<0.001) [FLAME].

Daily activities
ULTIBRO BREEZHALER 110/50 demonstrated a statistically superior improvement versus tiotropium in the percentage of 'days able to perform usual daily activities' over 26 weeks (8.45%, p<0.001) [SHINE] and showed numerical improvement over glycopyrronium (1.87; p=0.195) and statistical improvement over tiotropium (4.95; p=0.001) [SPARK].

COPD exacerbations
In the 64-week [SPARK] study comparing Ultibro Breezhaler 110/50 (n=729), glycopyrronium (n=739) and tiotropium (n=737), Ultibro Breezhaler 110/50 reduced the annualised rate of moderate or severe COPD exacerbations by 12% (95%CI -23%, -1%) compared to glycopyrronium and by 10% (95%CI -21%, 102%) compared to tiotropium. The number of moderate or severe COPD exacerbations/patient-years was 0.94 for Ultibro Breezhaler 110/50 (812 events), 1.07 for glycopyrronium (900 events) and 1.06 for tiotropium (898 events). The number of all COPD exacerbations/patient-years was 3.34 for Ultibro Breezhaler 110/50 (2,893 events), 3.92 for glycopyrronium (3,294 events) and 3.89 for tiotropium (3,301 events).

In a 52-week active-controlled [FLAME] study, ULTIBRO BREEZHALER 110/50 once daily met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate, or severe) compared to fluticasone/salmeterol. ULTIBRO BREEZHALER 110/50 further showed superiority in reducing the annualised rate of all exacerbations by 11% versus fluticasone/salmeterol (3.59 vs. 4.03, p=0.003) and prolonged time-to-first exacerbation with a 16% reduction in risk of an exacerbation (median time: 71 days for ULTIBRO BREEZHALER 110/50 vs. 51 days for fluticasone/salmeterol, p<0.001).

ULTIBRO BREEZHALER 110/50 reduced the annualised rate of moderate or severe exacerbations by 17% versus fluticasone/salmeterol (0.98 vs. 1.19, p<0.001) and prolonged time-to-first moderate or severe exacerbation with a 22% reduction in risk of an exacerbation (25th percentile: 127 days for ULTIBRO BREEZHALER 110/50 vs. 87 days for fluticasone/salmeterol, p<0.001). Less than 50% of patients in the ULTIBRO BREEZHALER 110/50 group had an exacerbation, therefore the time to the first moderate or severe exacerbation in the first quartile of patients was calculated instead.

ULTIBRO BREEZHALER 110/50 numerically reduced the annualised rate of severe exacerbations by 13% versus fluticasone/salmeterol (0.15 vs. 0.17, p=0.231). ULTIBRO BREEZHALER 110/50 prolonged time-to-first severe exacerbation with a 19% reduction in risk of an exacerbation (p=0.046).

The incidence of pneumonia (as confirmed by radiographic imaging i.e. chest x-ray or CT scan) was 3.2% in the ULTIBRO BREEZHALER 110/50 arm compared to 4.8% in the fluticasone/salmeterol arm (p=0.017). Time to first pneumonia was prolonged with ULTIBRO BREEZHALER 110/50 compared to fluticasone/salmeterol (p=0.013).

Use of rescue medication
Over 26 weeks, ULTIBRO BREEZHALER 110/50 once daily significantly reduced the use of rescue medication (salbutamol) by 0.96 puffs per day (p<0.001) compared to placebo and 0.54 puffs/day (p <0.001) compared to tiotropium in the [SHINE] study, as well as 0.39 puffs per day (p=0.019) compared to fluticasone/salmeterol in the [ILLUMINATE] study.

Over 64 weeks, ULTIBRO BREEZHALER 110/50 reduced the use of rescue medication (salbutamol) by 0.76 puffs per day (p<0.001) compared to tiotropium in the [SPARK] study.

Over 52 weeks, ULTIBRO BREEZHALER 110/50 once daily reduced the use of rescue medication by 1.01 puffs per day from baseline and fluticasone/salmeterol had a reduction of 0.76 puffs per day from baseline. The difference of 0.25 puffs per day was statistically significant (p<0.001).

Exercise tolerance
In a 3 week study [BRIGHT] where exercise tolerance was tested via cycle ergometry at submaximal (75%) workload (submaximal exercise tolerance test), ULTIBRO BREEZHALER 110/50, 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 significant improved (250 mL, p<0.001) compared to placebo. After three weeks of treatment, the improvement in inspiratory capacity with ULTIBRO BREEZHALER 110/50 was greater (320 mL, p<0.001) and exercise endurance time increased (59.5 seconds, p=0.006) compared to placebo. Similar findings were seen with tiotropium.

Whole-Body Plethysmography measurements of Residual volume (RV) and Functional Residual Capacity (FRC) give insights on airway closure and reflects the presence of gas trapping, considered a hallmark of COPD. On the first day of treatment, 60 min post-dose, ULTIBRO BREEZHALER 110/50 reduced RV by 380 mL (p<0.001) compared to placebo and FRC by 350 mL p< 0.001) compared to placebo. On day 21, 60 min post-dose, further reductions were seen with RV by 520 mL (p< 0.001) and FRC by 520 mL (p< 0.001).

5.2 Pharmacokinetic properties

Absorption
Indacaterol/glycopyrronium
Following inhalation of ULTIBRO BREEZHALER 110/50, the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.

Based on the in vitro performance data, the dose of indacaterol delivered to the lung is expected to be similar for ULTIBRO BREEZHALER 110/50 microgram and indacaterol 150 microgram monotherapy product. The steady-state exposure to indacaterol after ULTIBRO BREEZHALER 110/50 microgram inhalation was either similar or slightly lower than systemic exposure after indacaterol 150 microgram monotherapy product inhalation.

Absolute bioavailability of indacaterol after ULTIBRO BREEZHALER 110/50 microgram inhalation ranged from 47% to 66% whereas that of glycopyrronium was about 40%.
The steady-state exposure to glycopyrronium after ULTIBRO BREEZHALER 110/50 microgram inhalation was similar to systemic exposure after glycopyrronium 50 microgram monotherapy product inhalation.

Indacaterol
The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses.
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.

Distribution

Indacaterol

After intravenous infusion the volume of distribution (Vz) of indacaterol was 2,361 to 2,557 L indicating an extensive distribution. The in vitro human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Glycopyrronium

After i.v. dosing, the steady-state volume of distribution (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310 L, which reflects the much slower elimination after inhalation. The in vitro human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL. These concentrations were at least 6-fold higher than the steady state mean peaks levels achieved in plasma for a 50 micrograms once-daily dosing regimen.

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 drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides 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

In vitro metabolism studies showed consistent metabolic pathways for glycopyrronium bromide (glycopyrrolate) between animals and humans. No human specific metabolites were found.

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

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

After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since in vitro studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug Cmax and AUC) after i.v. administration, it is assumed that M9 is formed from the swallowed dose fraction of orally inhaled glycopyrronium bromide (glycopyrrolate) by pre-systemic hydrolysis and/or via first pass metabolism. After inhalation as well as i.v. administration, only minimal amounts of M9 were found in the urine (i.e. ≤ 0.5% of dose). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

In vitro inhibition studies demonstrated that glycopyrronium bromide (glycopyrrolate) has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. *In vitro* enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide (glycopyrrolate) for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

Elimination

Indacaterol

In clinical studies which included urine collection, 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. When compared with the serum clearance of indacaterol of 18.8 to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to 6% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

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 [3H]-labelled glycopyrronium bromide (glycopyrrolate) to humans, the mean urinary excretion of radioactivity in 48 h amounted to 85% of the dose. A further 5% of the dose was found in the bile. Thus, mass balance was almost complete.

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

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 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 a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 h after inhalation.

Linearity/non-linearity

Indacaterol

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.

Glycopyrronium

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.

Pharmacokinetics in special patient groups

ULTIBRO BREEZHALER

A population PK analysis in COPD patients after inhalation of ULTIBRO BREEZHALER 110/50 indicated no significant effect of age, gender and (lean body) weight on the systemic exposure to indacaterol and glycopyrronium. Lean body weight (which is a function of weight and height) was identified as a covariate. A negative correlation between systemic exposure and lean body-weight (or body weight) was observed; however, no dose adjustment is recommended due to the magnitude of the change or the predictive precision of lean body weight.

Smoking status and baseline FEV1 had no apparent effect on systemic exposure to indacaterol and glycopyrronium after inhalation of ULTIBRO BREEZHALER 110/50.

Indacaterol

A population analysis of the effect of age, gender and weight on systemic exposure in COPD patients after inhalation indicated that indacaterol can be used at the recommended dose in all age and weight groups and regardless of gender.

The pharmacokinetics of indacaterol was investigated in two different UGT1A1 genotypes – the fully functional [(TA)6, (TA)6] genotype and the low activity [(TA)7, (TA)7] genotype (Gilbert's syndrome genotype). The study demonstrated that steady-state AUC and Cmax of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

Glycopyrronium

A population PK analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Glycopyrronium 50 microgram once-daily can be used at the recommended dose in all age and body weight groups.
Gender, smoking status and baseline FEV1 had no apparent effect on systemic exposure.

Hepatic impairment
Based on the clinical PK characteristics of its monotherapy components, ULTIBRO BREEZHALER 110/50 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 mild and moderate hepatic impairment showed no relevant changes in Cmax or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

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

Renal impairment
Based on the clinical PK characteristics of its monotherapy components, ULTIBRO BREEZHALER 110/50 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 110/50 should be used only if the expected benefit outweighs the potential risk.

Indacaterol: Due to the very low contribution of the urinary pathway to total body elimination of indacaterol, a study in renally impaired subjects was not performed.

Glycopyrronium: Renal impairment has an impact on the systemic exposure to glycopyrronium. A moderate mean increase in total systemic exposure (AUC last) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease. Using a population PK analysis, it was concluded that in COPD patients with mild and moderate renal impairment (estimated glomerular filtration rate eGFR ≥30 mL/min/1.73 m2) glycopyrronium can be used at the recommended dose.

Race/Ethnicity
ULTIBRO BREEZHALER 110/50: When corrected by lean body weight, no statistically significant effect of ethnicity (Japanese versus non-Japanese) on exposure for both compounds was found.

Slightly higher total systemic exposures to indacaterol and glycopyrronium (on average 11% to 34% and 19% to 39%, respectively) were observed in Japanese compared to Caucasian healthy subjects after ULTIBRO BREEZHALER inhalation (at doses of 110/50 and 220/100 micrograms), which were not considered clinically relevant and did not raise any safety concerns.

Indacaterol: No difference between ethnic subgroups was identified. Limited treatment experience is available for the black population.

Glycopyrronium: There were no major differences in total systemic exposure (AUC) between Japanese and Caucasian subjects. Insufficient PK data is available for other ethnicities or races.

5.3 Preclinical safety data

Genotoxicity

Information related to indacaterol

Indacaterol was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosomal aberrations in Chinese hamster V79 cells and the rat bone marrow micronucleus test.

Information related to glycopyrronium

Glycopyrronium bromide (glycopyrrolate) was not genotoxic in assays for bacterial mutagenicity, chromosomal aberrations in vitro (human lymphocytes) or in vivo clastogenicity (rat bone marrow micronucleus test).

Carcinogenicity

No carcinogenicity studies have been conducted with indacaterol and glycopyrronium in combination.

Information related to indacaterol

The carcinogenic potential of indacaterol has been evaluated in a 26-week oral gavage study in transgenic mice (CB6F1/TgrasH2) and a 2-year inhalation study in rats. No carcinogenicity was observed in mice at doses up to 600mg/kg/day (approximately 200 times in males and 425-times in females the AUC in humans at the maximum recommended clinical dose of 110 µg/day with use of ULTIBRO BREEZHALER 110/50). Lifetime treatment of rats at 2.1 mg/kg/day (relative exposure, 57) resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β2-adrenergic agonist drugs. Their development is consistent with proliferation in response to prolonged relaxation of the smooth muscle (pharmacologically mediated), and the finding is not considered to indicate a carcinogenic hazard to patients. Squamous metaplasia was observed in the upper respiratory tract tissues of mice, rats and dogs following inhalation administration of indacaterol. This finding is consistent with an adaptive response to irritation and occurred at large multiples of the human dose. It is not considered to indicate a carcinogenic hazard to humans with the therapeutic use of indacaterol. No data are available to determine whether exposure to tobacco smoke enhances the respiratory tract toxicity of indacaterol.

Information related to glycopyrronium

Carcinogenicity studies of six months duration in transgenic mice (rasH2) using oral administration and 2 years duration in rats using inhalation administration revealed no evidence of carcinogenicity with glycopyrronium bromide (glycopyrrolate). The highest dose levels employed (75 and 100 mg/kg/day in male and female mice and 0.45 mg/kg/day in rats) were associated with systemic exposures (AUC) of approximately 53-fold higher in mice and 79-fold higher in rats than in humans at the maximum recommended dose of 50 µg once-daily. The lung deposited dose in rats (per unit alveolar surface area) was up to almost 200-fold higher than the level anticipated in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate
Magnesium stearate

Capsule shell components
Hypromellose, purified water, carrageenan, potassium chloride, FD&C Yellow 5/Tartrazine.

Black Printing Ink
Shellac, ethyl alcohol, isopropyl alcohol, propylene glycol, n-butyl alcohol, ammonium hydroxide, potassium hydroxide, water purified, iron oxide black

Blue Printing Ink
Shellac, ethyl alcohol, FD&C Blue 2, n-butyl alcohol, titanium dioxide, propylene glycol, isopropyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 degrees Celsius. Protect from moisture.

The capsules must always be stored in the original blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE.

6.5 Nature and contents of container

ULTIBRO BREEZHALER 110/50 hard capsules are for oral inhalation only. The pack is also supplied with a BREEZHALER inhalation device to permit oral inhalation of the contents of the capsule shell.

Pack sizes:
Carton containing 6 ULTIBRO 110/50 capsules and one BREEZHALER inhaler.
Carton containing 10 ULTIBRO 110/50 capsules and one BREEZHALER inhaler.
Carton containing 30 ULTIBRO 110/50 capsules and one BREEZHALER inhaler.
Multipack comprising 3 packs (each containing 30 ULTIBRO 110/50 capsules and one BREEZHALER inhaler)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each Ultibro Breezhaler 110/50 pack contains: one Ultibro Breezhaler inhaler device, and one or more blisters containing Ultibro Breezhaler capsules to be used in the inhaler.

For correct administration/use of the product, please refer to section 4.2.

Detailed instructions for use are provided in the package leaflet.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

8. DATE OF FIRST APPROVAL

16 October 2014

10. DATE OF REVISION OF THE TEXT

20 August 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	Update to 'Cardiovascular effects' section within Section 4.4 Special warnings and precautions for use
5.1	Update to 'QT interval' section within Section 5.1 Pharmacodynamic properties
8	Sponsor address updated