NISTAMI Inhaler (Indacaterol maleate + Glycopyrronium bromide)

Composition

NISTAMI® Inhaler
Active Substances
Each capsule contains:
Indacaterol Maleate equivalent to Indacaterol .... 110 micrograms
Glycopyrronium Bromide equivalent to Glycopyrronium ... 50 micrograms
Excipients
Lactose Monohydrate, Magnesium Stearate

Dosage Form

Inhalation powder

Description

NISTAMI® Inhaler contains a combination of indacaterol maleate and glycopyrronium bromide. Indacaterol is an ‘ultra’ long-acting beta_{2}-adrenergic agonist for once-daily administration. Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (anti-cholinergic) for once-daily maintenance bronchodilator treatment of chronic obstructive pulmonary disease (COPD).

Pharmacology

Mechanism of Action

NISTAMI® Inhaler
When indacaterol and glycopyrronium are administered together in NISTAMI® Inhaler, they provide additive efficacy due to their different mode of action targeting different receptors and pathways to achieve small muscle relaxation. Due to the differential density of beta_{2}-adrenoreceptors and M_{3}-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 lungs, 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}-adrenoreceptor agonists, including indacaterol, are, at least in part, attributable to stimulation of intracellular adenyly cyclase, the enzyme that catalyses 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
beta₁-receptors and 20-fold greater agonist activity compared to beta₃-receptors. This selectivity profile is similar to formoterol.

When inhaled, indacaterol acts locally in the lungs as a bronchodilator. Indacaterol is a nearly full agonist at the human beta₂-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although beta₂-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-adrenergic receptors are the predominant receptors in the human heart, there are also beta₂-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of beta₂-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective beta₂-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, M₂, and M₃ have a defined physiological function in the human lungs. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist of these three receptor subtypes. It demonstrated 4- to 5-fold selectivity for the human M₁ and M₂ receptors over the human M₃ 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 intravenous (IV) administration. Lung pharmacokinetic data in rats following inhalation of glycopyrronium bromide provides further evidence for this.

### Pharmacodynamics

**Primary Pharmacodynamic Effects**

The combination of indacaterol and glycopyrronium in NISTAMI® Inhaler showed a rapid onset of action within 5 minutes after dosing. The effect remains constant over the entire 24-hour dosing interval.

The mean bronchodilator effect derived from serial forced expiratory volume in one second (FEV₁) measurements over 24 hours was 0.32 L after 26 weeks of treatment when compared with placebo. The effect was significantly greater for NISTAMI® Inhaler when compared with 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 NISTAMI® Inhaler over time when compared with placebo or its monotherapy components.

**Secondary Pharmacodynamic Effects**

The systemic side effects of inhaled beta₂-adrenergic agonists and inhaled muscarinic receptor antagonists are the result of the activation of systemic beta₂-adrenergic receptors and blockade of muscarinic receptors after systemic absorption of the drugs. The side effect profile of NISTAMI® Inhaler 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 NISTAMI® Inhaler 440/200 micrograms administered in four-dose steps separated by 1 hour and compared with the effects of placebo, 600 micrograms indacaterol, 200 micrograms glycopyrronium and 200 micrograms salmeterol.

The largest time-matched heart rate increase for NISTAMI® Inhaler, compared with placebo, was +5.69 bpm, while the
largest decrease was –2.51 bpm. Overall, the effect on heart rate over time did not show a consistent pharmacodynamic effect of NISTAMI® Inhaler.

Whilst there were no significant effects when NISTAMI® Inhaler was compared with indacaterol and glycopyrronium alone, the heart rate seemed to be slightly higher (the largest difference being around 11 bpm) after inhalation of 200 micrograms of salmeterol.

Heart rate in COPD patients at supratherapeutic dose levels was investigated in NISTAMI® Inhaler up to doses of 150/100, 300/100 and 600/100 micrograms. There were no relevant effects of NISTAMI® Inhaler on mean heart rate over 24 hours and heart rate assessed after 30 minutes, 4 hours and 24 hours.

QT Interval
The components of NISTAMI® Inhaler (indacaterol and glycopyrronium) are not known to have a QT prolongation potential at clinical dose levels. 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 micrograms.

The effects of NISTAMI® Inhaler on the QTc interval were investigated in healthy volunteers after inhalation of NISTAMI® Inhaler 440/200 micrograms in four-dose steps separated by 1 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 NISTAMI® Inhaler 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 micrograms of NISTAMI® Inhaler also had no apparent influence on the QTc interval in repeated ECG assessments executed between 15 minutes and 24 hours after dosing. A slightly higher proportion of patients had QTc prolongations above 450 ms in the NISTAMI® Inhaler 600/100 micrograms group. The number of notable QTcF changes versus baseline (>30 ms) was similar across all active treatment groups (NISTAMI® Inhaler 600/100 micrograms, 300/100 micrograms and 150/100 micrograms, and indacaterol 300 micrograms), but was lower with placebo.

Serum Potassium and Blood Glucose
In healthy volunteers, after administration of NISTAMI® Inhaler 440/200 micrograms, the effect on serum potassium was very small (maximal difference, –0.14 mmol/L when compared with placebo). The maximal effect on blood glucose was 0.67 mmol/L. When NISTAMI® Inhaler 440/200 micrograms was compared with 200 micrograms 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).

Pharmacokinetics

Absorption
Following inhalation of NISTAMI® Inhaler, 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 lungs is expected to be similar for NISTAMI® Inhaler 110/50 micrograms and indacaterol 150 micrograms monotherapy product. The steady-state exposure to indacaterol after NISTAMI® Inhaler 110/50 micrograms inhalation was either similar or slightly lower than systemic exposure after indacaterol 150 micrograms monotherapy product inhalation.

Absolute bioavailability of indacaterol after NISTAMI® Inhaler 110/50 micrograms inhalation ranged from 47% to 66%, whereas that of glycopyrronium was about 40%.

The steady-state exposure to glycopyrronium after NISTAMI® Inhaler 110/50 micrograms inhalation was similar to systemic exposure after glycopyrronium 50 micrograms monotherapy product inhalation.

Indacaterol
The median time to reach peak serum concentrations of indacaterol was approximately 15 minutes 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-hour 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 micrograms and 600 micrograms.

**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, the pharmacokinetic steady-state of glycopyrronium was reached within 1 week of treatment. The steady-state mean peak and trough plasma concentrations of glycopyrronium for a 50 micrograms once-daily dosing regimen were 166 pg/mL and 8 pg/mL, respectively. With once-daily doses of 100 and 200 micrograms, 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 micrograms.

**Distribution**

**Indacaterol**

After IV infusion, the volume of distribution ($V_d$) 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 IV dosing, the steady-state volume of distribution ($V_{ss}$) of glycopyrronium was 83 L and the volume of distribution in the terminal phase ($V_z$) was 376 L. The apparent volume of distribution in the terminal phase following inhalation ($V_z/F$) 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 the total drug-related AUC over 24 hours. 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 metabolized 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 between animals and humans. No human specific metabolites were found. Hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis, resulting in the formation of a carboxylic acid derivative (M9) were seen. *In vitro* investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrronium. The hydrolysis to M9 is likely to be catalysed by members from the cholinesterase family.
After inhalation, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. Since in vitro studies did not show lung metabolism and M9 was of minor importance in the circulation (about 4% of parent drug C\text{max} and AUC) after IV administration, 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. After inhalation as well as IV administration, only minimal amounts of M9 were found in the urine (i.e. ≤0.5% of dose). Glucuronide and/or sulphate 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 OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. In vitro enzyme induction studies did not indicate a clinically relevant induction by glycopyrronium bromide for any of the CYP450 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/hour. When compared with the serum clearance of indacaterol of 18.8 to 23.3 L/hour, it is evident that renal clearance plays a minor role (about 2 to 6% of the systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the faecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human faeces 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 IV administration of -labelled glycopyrronium bromide to humans, the mean urinary excretion of radioactivity in 48 hours amounted to 85% of the dose. A further 5% of the dose was found in the bile. Thus, mass balance was almost complete.

Renal elimination of parent drug accounts for about 60 to 70% of the 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 micrograms glycopyrronium by healthy volunteers and patients with COPD, mean renal clearance of glycopyrronium was in the range of 17.4 and 24.4 L/hour. 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 IV (6.2 hours) and oral (2.8 hours) administration. The elimination pattern suggests a sustained lung absorption and/or transfer of glycopyrronium into the systemic circulation at and beyond 24 hours after inhalation.

**Linearity/Non-Linearity**

**Indacaterol**

Systemic exposure to indacaterol increased with increasing dose (150 to 600 micrograms) 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 the pharmacokinetic steady state increased about dose-proportionally over the dose range of 50 to 200 micrograms.

**Special Populations**

**NISTAMI® Inhaler**

A population pharmacokinetic analysis in COPD patients after inhalation of NISTAMI® Inhaler 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 NISTAMI® Inhaler.

**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 genotype and the low activity genotype (Gilbert’s syndrome genotype). The study demonstrated that steady-state AUC and Cₘ₉₉ of indacaterol were 1.2-fold higher in the genotype, indicating that systemic exposure to indacaterol is only insignificantly affected by this UGT1A1 genotypic variation.

**Glycopyrronium**

A population pharmacokinetic analysis of data in COPD patients identified body weight and age as factors contributing to inter-patient variability in systemic exposure. Glycopyrronium 50 micrograms 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.

**Race/Ethnicity**

**NISTAMI® Inhaler**: When corrected by lean body weight, no statistically significant effect of ethnicity (Japanese versus non-Japanese) on exposure for both compounds was found.

**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 pharmacokinetic data is available for other ethnicities or races.

### Indications

NISTAMI® Inhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms and reduce exacerbations in patients with COPD.

### Dosage And Administration

**General Target Population**

The recommended dosage of NISTAMI® Inhaler is the once-daily inhalation of the content of one 110/50 micrograms capsule using the NISTAMI® Inhaler.

**Special Populations**
Renal Impairment
NISTAMI® Inhaler 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, NISTAMI® Inhaler should be used only if the expected benefit outweighs the potential risk.

Hepatic Impairment
NISTAMI® Inhaler 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 Patients (Below 18 Years of Age)
NISTAMI® Inhaler should not be used in patients under 18 years of age.

Geriatric Patients (Aged 75 Years or Above)
NISTAMI® Inhaler can be used at the recommended dose in elderly patients aged 75 years and older.

Method of Administration
NISTAMI® Inhaler capsules must be administered only by the oral inhalation route and only using the NISTAMI® Inhaler. NISTAMI® Inhaler capsules must not be swallowed.
NISTAMI® Inhaler 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.
NISTAMI® Inhaler capsules must always be stored in the blister to protect from moisture, and only removed IMMEDIATELY BEFORE USE.
When prescribing NISTAMI® Inhaler, patients should be instructed on the 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.

Contraindications
NISTAMI® Inhaler is contraindicated in patients with hypersensitivity to indacaterol or glycopyrronium, which are components of NISTAMI® Inhaler, or to any of the excipients.

Warnings And Precautions

General
NISTAMI® Inhaler 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 NISTAMI® Inhaler belong.

Asthma
NISTAMI® Inhaler should not be used for the treatment of asthma due to the absence of data in this indication. Long-acting beta₂-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for the treatment of asthma.

Not for Acute Use
NISTAMI® Inhaler 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 NISTAMI® Inhaler. If signs suggesting allergic reactions occur, in particular, angio-oedema (including difficulties in breathing or swallowing, swelling of tongue, lips and face), urticaria, or skin rash, NISTAMI® Inhaler should be discontinued immediately and alternative therapy instituted.

Paradoxical Bronchospasm
As with other inhalation therapy, administration of NISTAMI® Inhaler may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, NISTAMI® Inhaler should be discontinued immediately and alternative therapy instituted.

**Anticholinergic Effects Related to Glycopyrronium**

Like other anticholinergic containing drugs, NISTAMI® Inhaler should be used with caution in patients with narrow-angle glaucoma or urinary retention.

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

**Systemic Effects of Beta-Agonists**

Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of NISTAMI® Inhaler at the recommended dose, as with other compounds containing a beta₂-adrenergic agonist, NISTAMI® Inhaler 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 beta₂-adrenergic agonists.

As with other drugs containing an inhaled beta₂-adrenergic agonist, NISTAMI® Inhaler should not be used more often or at higher doses than recommended.

**Cardiovascular Effects of Beta-Agonists**

Like other drugs containing a beta₂-adrenergic agonist, NISTAMI® Inhaler 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, the drug may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of QT interval, and ST segment depression, although the clinical significance of these findings is unknown.

Clinically relevant effects on prolongation of the QTc-interval have not been observed in clinical studies of NISTAMI® Inhaler at the recommended therapeutic dose.

**Hypokalaemia with Beta-Agonists**

Beta₂-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, hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias.

Clinically relevant effects of hypokalsemia have not been observed in clinical studies of NISTAMI® Inhaler at the recommended therapeutic dose.

**Hyperglycaemia with Beta-Agonists**

Inhalation of high doses of beta₂-adrenergic agonists may produce increases in plasma glucose. Upon initiation of treatment with NISTAMI® Inhaler, plasma glucose should be monitored more closely in diabetic patients. During long-term clinical studies ( and ), more patients on NISTAMI® Inhaler experienced clinically notable changes in blood glucose (4.9%) than on placebo (2.7%). NISTAMI® Inhaler has not been investigated in patients in whom diabetes mellitus is not well controlled.

Drug Interactions

**Interactions Linked to NISTAMI® Inhaler**

Concomitant administration of orally inhaled indacaterol and glycopyrronium under steady-state conditions of both drugs did not affect the pharmacokinetics of either drug.

No specific drug–drug interaction studies were conducted with NISTAMI® Inhaler. Information on the potential for interactions for NISTAMI® Inhaler is based on the potential for each of its two monotherapy components.
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.

**Beta-Adrenergic Blockers**

Beta-adrenergic blockers may weaken or antagonize the effect of beta₂-adrenergic agonists. Therefore, NISTAMI® Inhaler 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 the QTc Interval**

NISTAMI® Inhaler, as with other beta₂-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.

**Sympathomimetic Agents**

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

**Hypokalemia**

Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalemic effect of beta₂-adrenergic agonists.

**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 2-fold increase in AUC and 1.5-fold increase in C\textsubscript{max}. Co-administration of erythromycin with indacaterol resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2 fold for C\textsubscript{max}. 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 C\textsubscript{max}, 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 C\textsubscript{max} 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, ketoconazol, 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 1 year at doses of 600 micrograms.

Interactions Linked to Glycopyrronium

*In vitro* studies showed that glycypyrnonium 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 glycypyrnonium. Inhibition or induction of metabolism of glycypyrnonium is unlikely to result in a relevant change of systemic exposure to the drug.

**Anticholinergics**

The co-administration of NISTAMI® Inhaler 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 glycypyrnonium, increased total exposure (AUC) to glycypyrnonium 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.

### Renal Impairment

Based on the clinical pharmacokinetic characteristics of its monotherapy components, NISTAMI® Inhaler can be used at the recommended dose in patients with mild-to-moderate renal impairment. For patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m²), including those with end-stage renal disease requiring dialysis, NISTAMI® Inhaler should be used only if the expected benefit outweighs the potential risk. These patients should be monitored closely for potential adverse drug reactions.

**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 pharmacokinetic 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.

### Hepatic Impairment

Based on the clinical pharmacokinetic characteristics of its monotherapy components, NISTAMI® Inhaler 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 \( C_{\text{max}} \) or AUC of indacaterol, nor did protein-binding differ between mild and moderate hepatically 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. Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure.

### Women of Child-bearing Potential

There are no special recommendations for women of child-bearing potential.

### Pregnancy

There are no data from the use of NISTAMI® Inhaler in pregnant women. Likewise, there are no data from the use of either indacaterol or glycopyrronium in pregnant women.

No effects on the embryo or foetus were seen at any dose level of NISTAMI® Inhaler during an embryo-foetal development study in rats. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration. Reproductive toxicity was seen for indacaterol as an increased incidence of one skeletal variation following administration to rabbits. Glycopyrronium was not teratogenic in rats or rabbits following inhalational administration. In human parturients undergoing caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium bromide, umbilical plasma concentrations were low. The potential risk for humans is unknown. Therefore, as there is no adequate experience in pregnant women, NISTAMI® Inhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

### Lactation

It is not known whether indacaterol and/or glycopyrronium passes into human breast milk. Indacaterol and
glycopyrronium (including its metabolites) have been detected in the milk of lactating rats. Therefore, the use of NISTAMI® Inhaler by nursing mothers should only be considered if the expected benefit to the mother is greater than any possible risk to the infant.

Fertility

Information Related to Indacaterol and Glycopyrronium
Reproduction studies or other data in animals did not indicate a concern regarding fertility in either males or females.

Labour and Delivery

Information Related to Indacaterol
Like other beta₂-adrenergic agonist containing drugs, NISTAMI® Inhaler may inhibit labour due to a relaxant effect on uterine smooth muscle.

Undesirable Effects

The presentation of the safety profile of NISTAMI® Inhaler is based on the experience with NISTAMI® Inhaler and the individual monotherapy components.

Summary of the Safety Profile

The safety experience with NISTAMI® Inhaler comprised exposure of up to 15 months at the recommended therapeutic dose (110/50 micrograms).

The NISTAMI® Inhaler Phase III clinical development programme consisted of 11 studies and enrolled over 10,000 patients with a clinical diagnosis of moderate-to-very severe COPD. Safety data from nine of these studies with treatment durations of 4 weeks or longer were pooled from 4,352 patients exposed to NISTAMI® Inhaler 110/50 micrograms once daily.

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

At the recommended dose, the ADR profile of NISTAMI® Inhaler in patients with COPD showed clinically insignificant systemic effects of beta₂-adrenergic stimulation. Mean heart rate changes were less than one beat per minute, 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 hypokalaemia were similar to placebo.

Tabulated Summary of ADRs from Clinical Trials

ADRs are listed by MedDRA system organ class (Table 1). The frequency of ADRs was based on a pool of 3 Phase III placebo-controlled trials of 6 and 12 months in duration. The corresponding frequency category for each ADR 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).

NISTAMI® Inhaler showed similar ADRs as the individual monotherapy components. As NISTAMI® Inhaler 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 1 Kaplan-Meier cumulative incidence (%) of the ADRs at week 52 (placebo-controlled COPD pool)
<table>
<thead>
<tr>
<th>ADRs</th>
<th>Indacaterol/glyco-pyrronium 110/50 μg once daily</th>
<th>Placebo</th>
<th>Frequency category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,106 Rate (95% CI)</td>
<td>N=748 Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16.96 (14.53, 19.74)</td>
<td>19.64 (16.67, 23.06)</td>
<td>Very common</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9.03 (7.26, 11.20)</td>
<td>8.78 (6.77, 11.37)</td>
<td>Common</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.86 (1.91, 4.29)</td>
<td>1.49 (0.80, 2.75)</td>
<td>Common</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1.8 (1.11, 2.93)</td>
<td>1.54 (0.82, 2.88)</td>
<td>Common</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.86 (1.16, 2.99)</td>
<td>2.98 (1.16, 2.99)</td>
<td>Common</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2.06 (1.31, 3.21)</td>
<td>1.90 (1.04, 3.47)</td>
<td>Common</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia and diabetes mellitus</td>
<td>1.65 (0.92, 2.95)</td>
<td>2.42 (1.46, 4.00)</td>
<td>Common</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.81 (0.37, 1.76)</td>
<td>0.98 (0.44, 2.21)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.74 (1.05, 2.88)</td>
<td>0.95 (0.42, 2.14)</td>
<td>Common</td>
</tr>
<tr>
<td>Headache</td>
<td>3.24 (2.28, 4.60)</td>
<td>2.66 (1.64, 4.29)</td>
<td>Common</td>
</tr>
<tr>
<td>ADRs</td>
<td>Indacaterol/glyco-pyrronium 110/50 μg once daily N=1,106 Rate (95% CI)</td>
<td>Placebo N=748 Rate (95% CI)</td>
<td>Frequency category</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>0.09 (0.01, 0.64)</td>
<td>(0)</td>
<td>Rare</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma*</td>
<td>0.19 (0.05, 0.75)</td>
<td>(0)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>0.67 (0.32, 1.41)</td>
<td>0.78 (0.29, 2.12)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.8 (0.33, 1.95)</td>
<td>0.24 (0.03, 1.68)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.39 (0.15, 1.04)</td>
<td>0.7 (0.29, 1.66)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.73 (0.34, 1.56)</td>
<td>1.38 (0.68, 2.80)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>6.84 (5.38, 8.68)</td>
<td>5.94 (4.30, 8.17)</td>
<td>Common</td>
</tr>
<tr>
<td>Oropharyngeal pain, including throat irritation</td>
<td>2.95 (2.05, 4.23)</td>
<td>2.71 (1.70, 4.29)</td>
<td>Common</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0.28 (0.09, 0.85)</td>
<td>0.24 (0.03, 1.68)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Paradoxical bronchospasm</td>
<td>0.18 (0.05, 0.73)</td>
<td>0.51 (0.16, 1.64)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.29 (1.49, 3.51)</td>
<td>2.25 (1.32, 3.81)</td>
<td>Common</td>
</tr>
<tr>
<td>ADRs</td>
<td>Indacaterol/glyco-pyrronium 110/50 μg once daily N=1,106 Rate (95% CI)</td>
<td>Placebo N=748 Rate (95% CI)</td>
<td>Frequency category</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Dental caries</td>
<td>1.39 (0.79, 2.44)</td>
<td>0.97 (0.43, 2.19)</td>
<td>Common</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.64 (0.31, 1.34)</td>
<td>0.45 (0.14, 1.39)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0.28 (0.06, 1.18)</td>
<td>0.97 (0.43, 2.18)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/rash</td>
<td>0.56 (0.25, 1.25)</td>
<td>0.91 (0.37, 2.24)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0.92 (0.47, 1.81)</td>
<td>1.3 (0.60, 2.78)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>0.85 (0.41, 1.73)</td>
<td>0.44 (0.14, 1.37)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>0.74 (0.37, 1.47)</td>
<td>0.14 (0.02, 0.98)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.57 (0.25, 1.26)</td>
<td>0.53 (0.17, 1.70)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder obstruction and urinary retention</td>
<td>1.03 (0.52, 2.03)</td>
<td>(0)</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>1.96 (1.26, 3.05)</td>
<td>1.47 (0.79, 2.72)</td>
<td>Common</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1.85 (1.13, 3.02)</td>
<td>1.5 (0.77, 2.92)</td>
<td>Common</td>
</tr>
<tr>
<td>ADRs</td>
<td>Indacaterol/glyco-pyrronium 110/50 μg once daily</td>
<td>Placebo</td>
<td>Frequency category</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>N=1,106 Rate (95% CI)</td>
<td>N=748 Rate (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>0.65 (0.28, 1.48)</td>
<td>1.09 (0.51, 2.33)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.83 (0.41, 1.68)</td>
<td>0.54 (0.20, 1.43)</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Of the 1,106 patients on NISTAMI® Inhaler, 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.

* ADR observed with the combination NISTAMI® Inhaler but not with the monotherapy components.

### ADRs from Spontaneous Reports and Literature Cases (Frequency Not Known)

The following ADRs have been reported with NISTAMI® Inhaler in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is, therefore, categorized as not known. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

#### Table 2: ADRs from spontaneous reports and literature cases (frequency not known)

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Angio-oedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dysphonia</td>
<td></td>
</tr>
</tbody>
</table>

### Description of Selected ADRs

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 NISTAMI® Inhaler 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 NISTAMI® Inhaler for hypersensitivity and ischaemic heart disease were 2.06% versus 1.9% for placebo and 0.67% versus 0.78% for placebo, respectively.

### Overdosage

#### Information Related to NISTAMI® Inhaler
In a single-dose study in healthy volunteers; the 4-fold of the therapeutic dose of NISTAMI® Inhaler (four-dose steps of 110/50 micrograms separated by 1 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 micrograms of NISTAMI® Inhaler were inhaled over 2 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 micrograms of NISTAMI® Inhaler, but low prevalence and small patient numbers (N=49 and N=51 for 600/100 micrograms and 300/100 micrograms of NISTAMI® Inhaler, respectively) did preclude accurate analysis. In 4 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, hypokalaemia, and hyperglycaemia 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 hospitalized. 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 3,000 micrograms 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 micrograms 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 IV. administration of 150 micrograms glycopyrronium bromide (equivalent to 120 micrograms glycopyrronium) in healthy volunteers were respectively about 50-fold and 6-fold higher than the peak and total systemic exposure at steady state achieved with the recommended dose (50 micrograms once daily) of glycopyrronium and were well tolerated.

Non-Clinical Safety Data

Information Related to NISTAMI® Inhaler

A bridging toxicology program was performed for NISTAMI® Inhaler that included in vitro and in vivo safety pharmacology assessments, 2-week inhalation toxicity studies in rats and dogs, a 13-week inhalation toxicity study in dogs and an inhalation embryo-foetal development study in rats. Increased heart rates were apparent after the administration of each individual monotherapy and NISTAMI® Inhaler during cardiovascular safety pharmacology or repeated dose-toxicity studies in dogs. The effects on heart rate for NISTAMI® Inhaler increased in magnitude and duration when compared with the changes observed for each component alone consistent with an additive response. The highest doses of indacaterol administered alone or in the NISTAMI® Inhaler combination were associated with a similar incidence and severity of papillary muscle lesions in the heart of a few individuals during the 2-week toxicity study in dogs. Shortening of PR, P-width and QT that reflected increased heart rate and decreased systolic and diastolic blood pressure were also apparent following treatment with NISTAMI® Inhaler during the cardiovascular safety pharmacology study in dogs. An estimation of
the safety margin is based on papillary muscle lesions in the heart of dogs as the most sensitive species. The NOAEL of 0.386/0.125 mg/kg/day (indacaterol/glycopyrronium) in the 13-week toxicity study was devoid of heart lesions and corresponds with systemic exposures based on mean AUC\(_{0-24h}\) values of approximately 64 and 59-fold higher than seen in humans at a dose of 110/50 micrograms (indacaterol/glycopyrronium), for each component respectively.

Information Related to Indacaterol

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction. The effects of indacaterol seen in toxicity studies in dogs were mainly on the cardiovascular system and consisted of tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological effects and could be explained by the beta\(_2\)-agonistic properties of indacaterol. Other relevant effects noted in repeated-dose toxicity studies were mild irritancy of the upper respiratory tract in rats consisting of rhinitis and epithelial changes of the nasal cavity and larynx. All these findings were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Adverse effects with respect to fertility, pregnancy, embryonal/foetal development, pre- and postnatal development could only be demonstrated at doses more than 500-fold the daily inhalation dose of 150 micrograms in humans (based on AUC\(_{0-24h}\)). The effects, namely an increased incidence of one skeletal variation, were observed in rabbits. Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration. Studies on genotoxicity did not reveal any mutagenic or clastogenic potential. The carcinogenic potential of indacaterol has been evaluated in a 2-year inhalation study in rats and a 26-week oral transgenic mouse study. Lifetime treatment of rats resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle at doses approximately 30 times the dose of 150 micrograms once daily for humans (based on AUC\(_{0-24h}\)). Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other beta\(_2\)-adrenergic agonist drugs. A 26-week oral study in CB6F1/TgrasH2 hemizygous mice with indacaterol did not show any evidence of tumourigenicity at doses of at least 103 times the dose of 150 micrograms once daily for humans (based on AUC\(_{0-24h}\)).

Information Related to Glycopyrronium

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development. The effects seen during repeated-dose inhalation toxicity studies were attributable to exacerbations of the expected pharmacological action of glycopyrronium or mild local irritation. These included mild-to-moderate increases in heart rate in dogs and a number of reversible changes in rat and dogs associated with reduced secretions from the salivary, lacrimal and Harderian glands and pharynx. Lens opacities observed during chronic studies in rats have been described for other muscarinic antagonists and are considered to be species-specific changes with limited relevance for therapeutic use in patients. Findings in the respiratory tract of rats included degenerative/regenerative changes and inflammation in the nasal cavity and larynx that are consistent with mild local irritation. Minimal epithelial changes in the lung at the bronchioalveolar junction were also observed in rats and are regarded as a mild adaptive response. All these findings were observed at exposures considered to be sufficiently in excess of the maximum human exposure and, therefore, indicate limited relevance during clinical use.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium. Carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity at systemic exposures (AUC\(_{0-24h}\)) of approximately 53-fold higher in mice and 75-fold higher in rats than the dose of 50 micrograms once daily for humans. Published data for glycopyrronium do not indicate any reproductive toxicity issues. Glycopyrronium was not teratogenic.
in rats or rabbits following inhalation administration. Reproduction studies in rats and other data in animals did not indicate a concern regarding fertility in either males or females or pre- and post-natal development. Glycopyrronium and its metabolites did not significantly cross the placental barrier of pregnant mice, rabbits and dogs. Glycopyrronium (including its metabolites) was excreted into the milk of lactating rats and reached up to 10-fold higher concentrations in the milk than in the blood of the dam.

**Incompatibility**

Not Applicable

**Shelf-Life**

One and half years from the date of manufacturing.

**Storage And Handling Instructions**

See folding box. 
NISTAMI® Inhaler should not be used after the date marked “EXP” on the pack. 
NISTAMI® Inhaler must be kept out of the reach and sight of children.

**Packaging Information**

Each folding box contains 30 capsules and 1 inhaler. For further details, see the folding box. 
Manufacturer: 
A product of Novartis Pharma AG, Basel, Switzerland 
Information issued: India package insert dtd 20 Dec 16 based on the International Package Leaflet (IPL) dtd 14 Jul 16. 
™ = Trademark 
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Last updated: April 2017 
Last reviewed: April 2017

**NISTAMI Inhaler**

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