TRIOHALE Inhaler (Tiotropium bromide + Formoterol fumarate + Ciclesonide)

**Composition**

TRIOHALE Inhaler
Each puff contains:
Tiotropium Bromide monohydrate equivalent to
Tiotropium.................................................................9 mcg
Formoterol Fumarate Dihydrate IP.................................6mcg
Ciclesonide IP.................................................................200 mcg
Suspended in propellant HFA 227.................................q.s

**Dosage Forms**

Inhalation aerosol

**Description**

Tiotropium bromide is a long-acting, specific, muscarinic receptor antagonist, referred to as an anticholinergic. Formoterol is a potent long-acting selective beta\_2-receptor agonist, which acts by binding to the beta\_2 receptor in the airway. Ciclesonide is a synthetic glucocorticoid with a potent anti-inflammatory activity and weak mineralocorticoid activity.

The combination of Tiotropium, Formoterol and Ciclesonide will help in targeting different aspects of COPD viz. bronchodilation through different mechanisms and the inflammation with inhaled steroids.

**Pharmacology**

- **Pharmacodynamics**

  **Tiotropium**
  Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M\_1 to M\_5. In the airways, it exhibits pharmacological effects through inhibition of M\_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of Tiotropium is predominantly a site-specific effect.

  **Formoterol**
  Formoterol fumarate is a long-acting selective beta\_2-adrenergic receptor agonist (beta\_2-agonist). Inhaled Formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that Formoterol
has more than 200-fold greater agonist activity at beta_2-receptors than at beta_1-receptors. Although beta_2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta_1-receptors are the predominant receptors in the heart, there are also beta_2-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta_2-agonists may have cardiac effects.

The pharmacologic effects of beta_2-adrenoceptor agonist drugs, including Formoterol, 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 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that Formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Ciclesonide

Ciclesonide exhibits low binding affinity to the glucocorticoid-receptor. Once orally inhaled, Ciclesonide is enzymatically converted in the lungs to the principal metabolite (C21-des-methylpropionyl-Ciclesonide) which has a pronounced anti-inflammatory activity and is thus considered as the active metabolite.

Pharmacokinetics

Tiotropium

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) and from in-vitro experiments that Tiotropium bromide is poorly absorbed from the gastrointestinal tract (10-15%). Food is not expected to influence the absorption of this quaternary ammonium compound. Oral solutions of Tiotropium bromide have an absolute bioavailability of 2-3%. Maximum Tiotropium bromide plasma concentrations were observed five minutes after inhalation.

Distribution

The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 L/kg indicating the extensive binding to the tissues. At steady state, Tiotropium bromide plasma levels in COPD patients at peak were 17 - 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 3-4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that Tiotropium bromide does not penetrate the blood-brain barrier to any significant extent.

Metabolism

The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. The ester of tiotropium bromide is non-enzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (< 20% of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.

In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and
3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 2D6 and 3A4 are involved in metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

**Elimination**
The effective half-life of tiotropium ranges between 27-45 hours in COPD patients. After an intravenous dose in young healthy volunteers, total clearance was 880 mL/min. Intravenously administered tiotropium is mainly excreted unchanged in the urine (74%). After dry powder inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3 mcg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in the gut, which is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance (CrCl), indicating active secretion into the urine.

**Linearity / Nonlinearity**
Tiotropium bromide demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.

**Elderly Patients**
As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of Tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in the urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC₀₋₄h after inhalation), which was not significant when considered in relation to inter- and intra-individual variability.

**Hepatically-impaired Patients**
The effects of hepatic impairment on the pharmacokinetics of Tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on Tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

**Renally-impaired Patients**
Since Tiotropium is predominantly excreted renally, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and inhalation. Mild renal impairment (CL_cr of 50–80 mL/min), which is often seen in elderly patients, increased Tiotropium plasma concentrations (39% increase in AUC₀₋₄h after intravenous infusion). In COPD patients with moderate to severe renal impairment (CL_cr<50 mL/min), the intravenous administration of Tiotropium resulted in the doubling of plasma concentrations (82% increase in AUC₀₋₄h), which was confirmed by plasma concentrations after inhalation.

**Formoterol**

**Absorption**
Following inhalation of a single 120 mcg dose of Formoterol fumarate by 12 healthy subjects, Formoterol was rapidly absorbed into plasma, reaching a maximum drug concentration of 92 pg/mL within 5 minutes of dosing. In COPD patients treated for 12 weeks with Formoterol fumarate 12 or 24 mcg b.i.d., the mean plasma concentrations of Formoterol ranged between 4.0 and 8.8 pg/mL and 8.0 and 17.3 pg/mL, respectively, at 10 min, 2 h and 6 h post inhalation.

Studies in 10 healthy males investigating the cumulative urinary excretion of Formoterol and/or its (R, R) and (S, S)-enantiomers, after inhalation of dry powder (12-96 mcgs) or aerosol formulations (12-96 mcgs), showed that absorption increased linearly with the dose.
After 12 weeks administration of 12 mcg or 24 mcg Formoterol powder b.i.d., the urinary excretion of unchanged Formoterol increased by 63-73% in adult patients with asthma, by 19-38% in adult patients with COPD and by 18-84% in children, suggesting a modest and self-limiting accumulation of Formoterol in plasma after repeated dosing.

As reported for other inhaled drugs, it is likely that about 90% of Formoterol administered from an inhaler will be swallowed and then absorbed from the gastrointestinal tract. This means that the pharmacokinetic characteristics of the oral formulation largely apply also to the inhalation powder. When 80 mcg of 3H-labelled Formoterol fumarate was orally administered to two healthy volunteers, at least 65% of the drug was absorbed. The excreted amounts of Formoterol at steady-state were close to those predicted based on single-dose kinetics.

Oral doses of up to 300 micrograms of Formoterol are rapidly absorbed from the gastrointestinal tract. The peak plasma concentration of the unchanged substance is reached after 30 minutes to 1 hour. Repeated daily administration of 40 micrograms to 160 micrograms per day does not result in accumulation because of the short half-life. The pharmacokinetics of Formoterol does not differ significantly between men and women.

**Distribution**

The plasma protein binding of Formoterol is 61-64% (34% primarily to albumin). There is no saturation of binding sites in the concentration range reached with therapeutic doses.

**Metabolism**

Formoterol is eliminated primarily by metabolism, direct glucuronidation being the major pathway of biotransformation, with O-demethylation followed by further glucuronidation being another pathway. Minor pathways involve sulphate conjugation of Formoterol and deamidation followed by sulphate conjugation. Multiple isozymes catalyze the glucuronidation (UGT1A1, 1A3, 1A6, 1A7, 1A8, 1A9, 1A10, 2B7 and 2B15) and O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of Formoterol, and so consequently the potential for metabolic drug-drug interaction is low. Formoterol did not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to Formoterol or systemic adverse effects, has not been adequately explored. The kinetics of Formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism.

**Elimination**

Elimination of Formoterol from the circulation seems to be polyphasic; the apparent half-life depends on the time interval considered. On the basis of plasma or blood concentrations up to 6, 8 or 12 hours after oral administration, elimination half-life of about 2–3 hours was determined. From urinary excretion rates between 3 and 16 hours after inhalation, a half-life of about 5 hours was calculated.

Following oral administration of 80 mcg of radiolabeled Formoterol fumarate to 2 healthy subjects, 59%-62% of the radioactivity was eliminated in the urine and 32%-34% in the feces over a period of 104 hours. Renal clearance of Formoterol from blood in these subjects was about 150 mL/min. Following inhalation of a 12 mcg or 24 mcg dose by 16 patients with asthma, about 10% and 15%-18% of the total dose was excreted in the urine as unchanged Formoterol and direct conjugates of Formoterol, respectively. Following inhalation of 12 mcg or 24 mcg dose by 18 patients with COPD the corresponding values were 7% and 6-9% of the dose, respectively.

Based on plasma concentrations measured following inhalation of a single 120 mcg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. From urinary excretion rates measured in these subjects, the mean terminal elimination half-lives for the (R,R)- and (S,S)-enantiomers were determined to be 13.9 and 12.3 hours, respectively. The (R,R)- and (S,S)-enantiomers
represented about 40% and 60% of unchanged drug excreted in the urine, respectively, following single inhaled doses between 12 and 120 mcg in healthy volunteers and single and repeated doses of 12 and 24 mcg in patients with asthma. Thus, the relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

**Ciclesonide**

### Absorption

Studies with oral and intravenous dosing of radiolabeled Ciclesonide have shown an incomplete extent of oral absorption (24.5%). The oral bioavailability of both Ciclesonide and the active metabolite is negligible (<0.5% for Ciclesonide, <1% for the metabolite). Based on a gamma-scintigraphy experiment, lung deposition in healthy subjects is 52%. In line with this figure, the systemic bioavailability for the active metabolite is >50% by using the Ciclesonide metered dose inhaler. As the oral bioavailability for the active metabolite is <1%, the swallowed portion of the inhaled Ciclesonide does not contribute to systemic absorption.

### Distribution

Following intravenous administration to healthy subjects, the initial distribution phase for Ciclesonide was rapid and consistent with its high lipophilicity. The volume of distribution averaged 2.9 L/kg. The total serum clearance of Ciclesonide is high (average 2.0 L/hr/kg) indicating a high hepatic extraction. The percentage of Ciclesonide bound to human plasma proteins averaged 99%, and that of the active metabolite 98-99%, indicating an almost complete binding of circulating Ciclesonide/active metabolite to plasma proteins.

### Metabolism

Ciclesonide is primarily hydrolysed to its biologically active metabolite by esterase enzymes in the lung. Investigation of the enzymology of further metabolism by human liver microsomes showed that this compound is mainly metabolized to hydroxylated inactive metabolites by CYP3A4 catalysis. Furthermore, reversible lipophilic fatty acid ester conjugates of the active metabolite were detected in the lung.

### Elimination

Ciclesonide is predominantly excreted via the faeces (67%), after oral and intravenous administration, indicating that excretion via the bile is the major route of elimination.

### Indications

Symptomatic treatment of patients with severe COPD (FEV₁ < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

### Dosage & Administration

#### TRIOHALE Inhaler

**Adults**

The recommended dosage is the inhalation of two puffs, once daily. TRIOHALE Inhaler may be used with a Zerostat/Zerostat VT Spacer device in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

### Contraindications
TRIOHALE Inhaler should not be used in patients with hypersensitivity to Tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxictrorpium, Formoterol fumarate or Ciclesonide or to the excipients in the inhaler.

**Warnings & Precautions**

**General**

As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, TRIOHALE Inhaler should be discontinued immediately and alternative therapy substituted.

TRIOHALE Inhaler, as a once daily maintenance treatment for COPD, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.

TRIOHALE Inhaler should not be used more frequently than once daily.

As the combination contains Tiotropium + Formoterol + Ciclesonide, the warnings and precautions of each of the components of the combination should be followed.

**Tiotropium**

Consistent with its anticholinergic activity, Tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤50 mL/min) Tiotropium bromide should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment.

Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Should any combination of these eye symptoms develop, patients should stop using TRIOHALE Inhaler and consult a specialist immediately. Dry mouth, which has been observed with anticholinergic treatment, may in the long term be associated with dental caries.

Tiotropium bromide should not be used more frequently than once daily.

Immediate hypersensitivity reactions, including angio edema, may occur after administration of Tiotropium. If such a reaction occurs, therapy with TRIOHALE Inhaler should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including Tiotropium, may cause paradoxical bronchospasm. If this occurs, treatment with TRIOHALE Inhaler should be stopped and other treatments considered.

**Formoterol**

It should not be initiated in patients with significantly worsening, acutely deteriorating, or potentially life-threatening episodes of asthma or COPD. The use of Formoterol in this setting is not appropriate.

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

When beginning treatment with Formoterol, patients who have been taking inhaled, short-acting beta,agonistson a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute symptoms.

Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving Formoterol when the following conditions may exist: Ischaemic heart disease, cardiac arrhythmias,
especially third degree atrioventricular block, severe cardiac decompensation, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, thyrotoxicosis, known or suspected prolongation of the QT interval (QTc > 0.44 sec) and in patients treated with drugs affecting the QT interval. Formoterol itself may induce prolongation of QT interval. Caution should be used when co-administering theophylline and Formoterol in patients with pre-existing cardiac conditions.

Due to the hyperglycaemic effect of beta₂-stimulants, additional blood glucose controls are recommended in diabetic patients.

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

As with other inhalation therapy there is a risk of paradoxical bronchospasm. If paradoxical bronchospasm occurs, Formoterol should be discontinued immediately and alternative therapy instituted.

Immediate hypersensitivity reactions may occur after administration of Formoterol, as demonstrated by cases of anaphylactic reactions, urticaria, angioedema, rash, and bronchospasm.

**Ciclesonide**

As with all inhaled corticosteroids, Ciclesonide should be administered with caution in patients with active or quiescent pulmonary tuberculosis, fungal, viral or bacterial infections, and only if these patients are adequately treated.

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma.

There is no data available in patients with severe hepatic impairment. An increased exposure in patients with severe hepatic impairment is expected and these patients should therefore be monitored for potential systemic effects.

These patients may require specialised advice to determine the extent of adrenal impairment before elective procedures. The possibility of residual impaired adrenal response should always be considered in an emergency (medical or surgical) and elective situations likely to produce stress, and appropriate corticosteroid treatment considered.

Concomitant treatment with ketoconazole or other potent CYP3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

The benefits of inhaled Ciclesonide should minimise the need for oral steroids. However, patients transferred from oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to inhaled Ciclesonide. The possibility of respective symptoms may persist for some time.

For the transfer of patients being treated with oral corticosteroids:

The transfer of oral steroid-dependent patients to inhaled Ciclesonide, and their subsequent management, needs special care as recovery from impaired adrenocortical function, caused by prolonged systemic steroid therapy, may take a considerable time.

Patients, who have been treated with systemic steroids for long periods of time, or at a high dose, may have adrenocortical suppression. With these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously.

After approximately a week, gradual withdrawal of the systemic steroid is started by reducing the dose by 1 mg prednisolone per week, or its equivalent. For maintenance doses of prednisolone in excess of 10 mg daily, it may be appropriate to cautiously use larger reductions in dose at weekly intervals.
Some patients feel unwell in a non-specific way during the withdrawal phase despite maintenance or even improvement of respiratory function. They should be encouraged to persevere with inhaled Ciclesonide and to continue withdrawal of systemic steroid, unless there are objective signs of adrenal insufficiency. Patients transferred from oral steroids whose adrenocortical function is still impaired should carry a steroid warning card indicating that they need supplementary systemic steroid during periods of stress, e.g. worsening asthma attacks, chest infections, major intercurrent illness, surgery, trauma, etc. Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies such as allergic rhinitis or eczema previously controlled by systemic drug. Paradoxical bronchospasm with an immediate increase of wheezing or other symptoms of bronchoconstriction after dosing should be treated with an inhaled short-acting bronchodilator, which usually results in quick relief. The patient should be assessed and therapy with Ciclesonide should only be continued, if after careful consideration the expected benefit is greater than the possible risk.

### Drug Interactions

There has been no clinical trial performed to study the interactions of various drugs with TRIOHALE Inhaler, however the interactions of the individual components of the combination should be kept in mind before prescribing TRIOHALE Inhaler.

**Tiotropium**

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

The co-administration of Tiotropium bromide with other anticholinergic-containing drugs has not been studied and is therefore not recommended.

**Formoterol**

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the pharmacologically predictable sympathetic effects of Formoterol may be potentiated. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonist with non-potassium sparing diuretics.

Formoterol, as with other beta2-agonists, should be administered with extreme caution to patients being treated with monamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Beta-adrenergic receptor antagonists (beta-blockers) and Formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta2-agonists, such as Formoterol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.
Ciclesonide

In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of Ciclesonide \( M_1 \) in man. In a drug-drug interaction study at steady state with Ciclesonide and ketoconazole as a potent CYP3A4 inhibitor, the exposure to the active metabolite \( M_1 \) increased approximately 3.5-fold, whereas the exposure to Ciclesonide was not affected. Therefore the concomitant administration of potent inhibitors of CYP 3A4 (e.g. ketoconazole, itraconazole and ritonavir or nelfinavir) should be avoided unless the benefit outweighs the increased risk of systemic side effects of corticosteroids.

## Renal Impairment

Tiotropium bromide being a predominantly renally excreted drug, patients with moderate to severe renal impairment (\( \text{CL}_{\text{cr}} \) of < 50 mL/min) treated with TRIOHALE Inhaler should be monitored closely. The pharmacokinetics of Formoterol has not been studied in subjects with renal impairment. There is no need to adjust the dose of Ciclesonide in patients with renal impairment.

## Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of Tiotropium were not studied. However, hepatic impairment is not expected to have relevant influence on Tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors. The pharmacokinetics of Formoterol has not been studied in subjects with hepatic impairment. There is no need to adjust the dose of Ciclesonide in patients with hepatic impairment.

## Pregnancy

There are no adequate and well-controlled studies of Tiotropium, Formoterol or Ciclesonide in pregnant women. As with any medicine, use of TRIOHALE Inhaler during pregnancy should only be considered if the expected benefit to the mother is greater than any risk to the foetus.

## Lactation

It is unknown whether inhaled Tiotropium, Formoterol or Ciclesonide is excreted in human breast milk. Administration of TRIOHALE Inhaler to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

## Undesirable Effects

As the combination contains Tiotropium + Formoterol + Ciclesonide, the type and severity of side effects associated with each of the components may be expected.

### Tiotropium

Several organ systems and functions are under the control of the parasympathetic nervous system and, therefore, can be affected by anticholinergic agents. Possible adverse events attributable to systemic anticholinergic effects include dry mouth, dry throat, increased heart rate, blurred vision, glaucoma, urinary difficulty, urinary retention, and constipation.

The most common anticholinergic adverse reaction reported by COPD patients was dry mouth, which was mild in the majority of cases. In general, dry mouth had an onset of 3 and 5 weeks, which resolved while patients continued to receive Tiotropium bromide.

The adverse events seen include Body as a whole: chest pain (non-specific), and edema (dependent), allergic reaction, leg pain; Gastrointestinal system disorders: abdominal pain, constipation, dry mouth, dyspepsia, vomiting; gastro esophageal reflux disease, gastrointestinal disorder not otherwise specified (NOS),
oropharyngeal candidiasis, intestinal obstruction, including ileus paralytic, gingivitis, glossitis, dysphagia, stomatitis (including ulcerative stomatitis), nausea, dental caries; Musculoskeletal and connective tissue disorders: myalgia, skeletal pain, joint swelling; resistance mechanism disorders: infection (herpes zoster), moniliasis; Respiratory thoracic and mediastinal disorders: oral candidiasis, throat irritation, dysphonia, cough, bronchospasm, laryngitis, epistaxis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection; Skin and subcutaneous tissue disorders, immune system disorders: rash, urticaria, pruritus, hypersensitivity (including immediate reactions), angioedema, skin infection, skin ulcer, dry skin; Renal and urinary disorders: dysuria, urinary retention, urinary tract infection; Eye disorders: vision blurred, glaucoma, intraocular pressure increased, cataract; Metabolism and nutrition disorders: dehydration; Nervous system disorders: dizziness, headache, insomnia, paresthesia, taste disorders; Cardiac disorders: tachycardia, palpitations, supraventricular tachycardia, atrial fibrillation, angina pectoris (including aggravated angina pectoris); Psychiatric disorder: depression.

In addition, the following adverse reactions have also been identified during worldwide post-approval use of Tiotropium bromide: mouth ulceration, and pharyngolaryngeal pain), dysphagia, and hoarseness.

Formoterol

Overall adverse events that occur with >1% incidence: viral infection, bronchitis, chest pain, tremors, dizziness, insomnia, tonsillitis, rash, and dysphonia. Adverse events occurring in more than 1% of patients with COPD: upper respiratory tract infection, pain back, pharyngitis, pain chest, sinusitis, fever, cramps in muscles and leg, anxiety, pruritus, increased sputum and dry mouth. Other adverse events seen include dysphonia, myalgia, and tremor.

Rare reports of anaphylactic reactions, including severe hypotension and angioedema; angina pectoris, prolongation of QTc interval, variation in blood pressure, taste disturbance, nausea, exanthema, peripheral oedema have also been received in association with the use of Formoterol fumarate. Other adverse reactions to Formoterol are similar in nature to other selective beta₂-adrenoceptor agonists; e.g., angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, nausea, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.

Treatment with beta₂-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Ciclesonide

Paradoxical bronchospasm is the most common adverse event seen with Ciclesonide. It may occur immediately after dosing and is an unspecific acute reaction to all inhaled medications, which may be related to the drug, the excipient, or evaporation cooling in the case of metered dose inhalers. In the majority of cases, this reaction is mild and does not require the withdrawal of the drug. Some of the uncommon side effects seen with Ciclesonide (>1/1,000 – <1/100) are nausea and vomiting, application site reactions, bad taste, application site dryness; rash and eczema, cough after inhalation, oral fungal infections, headache, dysphonia and paradoxical bronchospasm. Other rare side effects (1/10,000 – 1/1,000) include palpitations, abdominal pain, dyspepsia, angioedema, hypersensitivity and hypertension. Unknown side effects include psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioral changes and hypertension.

Nausea, vomiting, oral fungal infections, cough after inhalation, paradoxical bronchospasm, abdominal pain and dyspepsia had a similar or lower incidence compared with placebo. Palpitations were observed in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol).

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged
periods. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, and glaucoma.

### Overdosage

There is no data on overdosage with the combination of Tiotropium, Formoterol and Ciclesonide.

#### Tiotropium

High doses of Tiotropium bromide may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg of Tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following a 7-day dosing of up to 170 mcg of Tiotropium bromide in healthy volunteers. In a multiple-dose study in COPD patients with a maximum daily dose of 43 mcg of Tiotropium bromide over 4 weeks, no significant undesirable effect has been observed. Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.

#### Formoterol

The expected signs and symptoms with overdosage of Formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms e.g., angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia and insomnia. Metabolic acidosis may also occur. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of Formoterol. The preferred antidotes are other cardioselective beta₂-blocking agents, but these should be used with caution in patients with a history of bronchospasm.

#### Ciclesonide

Inhalation by healthy volunteers of a single dose of 3600 mcg of Ciclesonide was well tolerated. The potential for acute toxic effects following overdose of inhaled Ciclesonide is low. After acute overdosage no specific treatment is necessary. After prolonged administration of 1600 mcg of Ciclesonide, no clinical signs of adrenal suppression were observed. However, if higher than recommended dosage is continued over prolonged periods, some degree of adrenal suppression cannot be excluded. Monitoring of adrenal reserve may be necessary.

### Packaging Information

TRIOHALE Inhaler.... Each canister contains 120 metered doses.

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TRIOHALE Inhaler

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