Cipla

Tiotropium Bromide, Formoterol Fumarate & Ciclesonide Inhaler

Triohale-T inhaler

with **dose indicator**

patient information leaflet

please read this leaflet completely before use

Triohale-T inhaler

21051659

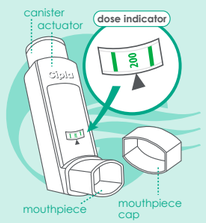
Triohale-T inhaler

21051659

CFC - FREE

ABOUT YOUR TRIOHALE-T INHALER

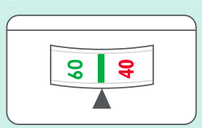
PARTS OF THE INHALER



Your **TRIOHALE-T** inhaler now comes with a dose indicator. It shows the number of puffs in the inhaler. As you use the inhaler, the dose indicator will countdown and indicate the number of puffs remaining.

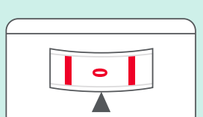
HOW TO KNOW THAT YOUR TRIOHALE-T INHALER IS GETTING OVER

When there are 40 puffs remaining, the colour of the numbers will change from green to red.



This indicates that fewer doses are remaining in the inhaler. You should now consider getting a new inhaler or ask your doctor if you need another one.

When the dose indicator displays '0', this means that there is no more medicine left in the inhaler & you need to discard the inhaler. Your inhaler may not feel empty & it may continue to operate, but you will not get the right amount of medicine, if you keep using it beyond '0'.



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SUMMARY OF PRODUCT CHARACTERISTICS OF TRIOHALE-T INHALER (CFC FREE)

1. NAME OF THE MEDICINAL PRODUCT

Triohale-T Inhaler (CFC FREE) 200 MD

(Tiotropium bromide, formoterol fumarate and ciclesonide)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation delivers:
Tiotropium Bromide Monohydrate BP Equivalent to Tiotropium.....9 mcg
Formoterol Fumarate Dihydrate Ph. Eur.....6 mcg
Ciclesonide.....200 mcg
Suspended in Propellent HFA 227.....q.s

3. PHARMACEUTICAL FORM

Metered dose Inhaler

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of patients with severe COPD (FEV 1< 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

4.2 Posology and method of administration

Adults

The recommended dosage is the inhalation of two puffs, once daily. This inhaler may be used with a spacer device in patients who find it difficult to synchronize aerosol actuation with inspiration of breath.

4.3 Contraindications

Triohale-T Inhaler is contraindicated in patients with hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium, Formoterol fumarate or Ciclesonide or to the excipients in the inhaler.

4.4 Special warnings and precautions for use

Tiotropium bromide

Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.

Immediate hypersensitivity reactions may occur after administration of tiotropium bromide inhalation.

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. (see section 4.8). Inhaled medicines may cause inhalation-induced bronchospasm.

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

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 (see section 5.2).

Patients should be cautioned to avoid getting the drug come in contact with 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 coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using tiotropium bromide and consult a specialist immediately.

Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

Tiotropium bromide should not be used more frequently than once daily (see section 4.9).

Formeterol fumarate

Formeterol fumarate should not be used (and is not sufficient) as the first treatment for asthma.

Asthmatic patients who require therapy with long-acting β_2-agonists, should also receive optimal maintenance anti-inflammatory therapy with corticosteroids. Patients must be advised to continue taking their anti-inflammatory therapy after the introduction of formoterol even when symptoms decrease. Should symptoms persist, or treatment with β_2- agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy.

Although formeterol fumarate may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on formeterol fumarate during an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Serious asthma-related adverse events and exacerbations may occur during treatment with formeterol fumarate. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of formeterol fumarate.

Formeterol fumarate should be used strictly in accordance with the dosage recommendations. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of formeterol fumarate.

Regular review of patients as treatment is stepped down is important. The lowest effective dose of formeterol fumarate should be used.

The maximum daily dose should not be exceeded.

A sudden and progressive deterioration of the asthmatic disorder can be life-threatening and requires immediate medical intervention. Considerably exceeding the prescribed individual doses or the total daily dose can be hazardous due to the effects on the heart (cardiac arrhythmia, rise in blood pressure), in combination with changes in the salt concentrations in body fluids (electrolyte shifts), and must therefore be avoided.

Concomitant conditions

Caution should be observed when treating patients with third degree atrioventricular block, refractory diabetes mellitus, thyrotoxicosis, phaeochromocytoma, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure and occlusive vascular diseases, especially arteriosclerosis.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval, eg. Congenital or drug-induced (QTc > 0.44 seconds) and in patients treated with drugs affecting the QTc-interval (see section 4.5).

Due to the hyperglycaemic effects of β_2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

If anaesthesia with halogenated anaesthetics is planned, it should be ensured that formeterol fumarate is not administered for at least 12 hours before the start of anaesthesia.

Paradoxical bronchospasm

As with every inhalation therapy, the potential for paradoxical bronchospasm should be considered. If it occurs, the treatment should be discontinued immediately and alternative therapy started (see section 4.8).

Hypokalaemia

Potentially serious hypokalaemia may result from β_2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatment with xanthine-derivatives, steroids and diuretics. The serum potassium levels should therefore be monitored.

Therefore potassium levels have to be regularly monitored particularly in patients with low basic potassium values or peculiar risks for decreased blood potassium levels. The monitoring should also be conducted if no decreased levels occurred under previous treatment with short acting β_2-sympathomimetics. Where applicable, potassium has to be substituted.

Due to decreased serum potassium levels the effect of digitalis containing medicinal products is enhanced.

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.

As with all inhaled corticosteroids, ciclesonide is not indicated in the treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

As with all inhaled corticosteroids, ciclesonide is not designed to relieve acute asthma symptoms for which an inhaled short-acting bronchodilator is required. Patients should be advised to have such rescue medication available.

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, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

It is recommended that the height of children and adolescents receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of inhaled corticosteroid, if possible to the lowest dose at which effective control of asthma is maintained. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

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.

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.

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.

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. Correlation between severity of asthma and general susceptibility for acute bronchial reactions should be kept in mind (see section 4.8).

Patients inhaler technique should be checked regularly to make sure that inhaler actuation is synchronised with inhaling to ensure optimum delivery to the lungs.

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 (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Tiotropium bromide

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, anti-IgE treatment without clinical evidence of drug interactions.

Use of LABA or ICS was not found to alter the exposure to tiotropium.

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

Formeterol fumarate

No specific interaction studies have been carried out with formoterol.

There is a theoretical risk that concomitant treatment with other drugs known to prolong the QTc-interval may give rise to a pharmacodynamic interaction with formoterol and increase the possible risk of ventricular arrhythmias. Examples of such drugs include certain antihistamines (e.g. terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin and tricyclic antidepressants.

Concomitant administration of other sympathomimetic substances such as other β_2-agonists or ephedrine may potentiate the undesirable effects of formoterol fumarate and may require titration of the dose.

The simultaneous use of formoterol and theophylline can result in mutual potentiation of effects, and there is also the likelihood of increased undesirable effects such as cardiac dysrhythmia. Compounds which themselves potentiate sympathomimetic effects, such as L-dopa, L-thyroxine, oxytocin or alcohol, can also affect cardiovascular regulation when taken at the same time as formoterol.

Administration of formoterol fumarate to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants should be performed with caution, since the action of β2-adrenergic stimulants on the cardiovascular system may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics such as thiazides and loop diuretics may potentiate a rare hypokalaemic adverse effect of β_2-agonists. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs. ß -adrenergic blockers may weaken or inhibit the effect of formoterol fumarate.

Therefore, formoterol fumarate should not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

Ciclesonide

In vitro data indicate that CYP3A4 is the major enzyme involved in the metabolism of the active metabolite of ciclesonide M1 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 M1 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.

4.6 Pregnancy, lactation and Fertility

Pregnancy

There are no adequate and well-controlled studies of Tiotropium, Formoterol or Ciclesonide in pregnant women. As with any medicine, use of tiotropium bromide, formoterol fumarate and ciclesonide 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 tiotropium bromide, formoterol fumarate and ciclesonide 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.

Fertility

Clinical data on fertility are not available for tiotropium.

4.7 Effects on ability to drive and use machines

Tiotropium bromide

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness, blurred vision, or headache may influence the ability to drive and use machinery.

Formeterol fumarate

Formeterol fumarate has no influence on the ability to drive and use machines.

Ciclesonide

Inhaled ciclesonide has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects:

Tiotropium bromide

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium bromide.

Tabulated summary of adverse reactions

The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group (9,647 patients) from 28 pooled placebo-controlled clinical trials with treatment periods ranging from four weeks to four years.

Frequency is defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class / MedDRA Preferred Term Frequency

Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare
Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

Description of selected adverse reactions

In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 4% of patients.

In 28 clinical trials, dry mouth led to discontinuation in 18 of 9,647 tiotropium treated patients (0.2%).

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation and intestinal obstruction including ileus paralytic as well as urinary retention.

Other special population

An increase in anticholinergic effects may occur with increasing age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Formeterol fumarate

The most commonly reported adverse events of β_2-agonist therapy, such as tremor and palpitations, tend to be mild and disappear within a few days of treatment.

Adverse reactions, which have been associated with formoterol, are listed below by system organ class and frequency. Frequency is defined as: Very Common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10000, <1/1000), Very rare (<1/10000)

System organ Class	Adverse Reaction	Frequency
Blood and lymphatic system disorders	Thrombopenia	Very rare
Immune system disorders	Hypersensitivity reactions, e.g. angioedema, bronchospasm, exanthema, urticaria, pruritus.	Rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
Psychiatric disorders:	Agitation, restlessness, sleep disorder	Uncommon
	Abnormal behaviour, hallucination	Very rare
Nervous system disorders	Tremor, headache	Common
	Dizziness, taste disturbances	Uncommon
	Central nervous system stimulation	Very rare
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles, Angina pectoris	Rare
	Prolongation of QTc interval	Very rare
Vascular disorders	Variation in blood pressure	Rare
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Throat irritation	Uncommon
	Bronchospasm paradoxical (see section 4.4)	Rare
	Dyspnoea, exacerbation of asthma	Very rare
Gastrointestinal disorders	Nausea	Uncommon
Skin and subcutaneous tissue disorders	Hyperhidrosis	Uncommon
Musculoskeletal and connective tissue disorders	Muscle cramps, myalgia	Uncommon
Renal and urinary disorders	Nephritis	Rare
General disorders and administration site conditions	Oedema peripheral	Very rare

Nausea, dysgeusia, throat irritation, hyperhidrosis, restlessness, headache, dizziness and muscle cramps may resolve spontaneously within one to two weeks of continued treatment.

Central nervous system stimulating effects have been sporadically reported following inhalation of β_2-sympathomimetics, manifesting as hyperexcitability. These effects were mainly observed in children up to 12 years of age.

Treatment with β_2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Ciclesonide

Approximately 5% of patients experienced adverse reactions in clinical trials with Ciclesonide given in the dose range 40 to 1280 micrograms per day. In the majority of cases, these were mild and did not require discontinuation of treatment with Ciclesonide.

Frequency	Uncommon	Rare	Unknown
System Organ Class	(>1/1,000, <1/100)	(1/10,000 – 1/,1000)	
Cardiac Disorders		Palpitations**	
Gastrointestinal Disorders	Nausea, vomiting* Bad taste	Abdominal pain* Dyspepsia*	
General disorders and administration site conditions	Application site reactions Application site dryness		
Immune System Disorders		Angioedema Hypersensitivity	
Infections and infestations	Oral fungal infections*		
Nervous System Disorders	Headache*		
Psychiatric Disorders			Psychomotor hyperactivity, sleep disorders, anxiety, depression, aggression, behavioural changes (predominantly in children)
Respiratory, thoracic and mediastinal disorders	Dysphonia Cough after inhalation* Paradoxical bronchospasm*		
Skin and subcutaneous tissue disorders	Eczema and rash		
Vascular disorders		Hypertension	

* Similar or lower incidence when compared with placebo

** Palpitations were observed in clinical trials in cases mostly confounded with concomitant medication with known cardiac effects (e.g. theophylline or salbutamol).

Paradoxical bronchospasm may occur immediately after dosing and is an unspecific acute reaction to all inhaled medicinal products, which may be related to the active substance, the excipient, or evaporation cooling in the case of metered dose inhalers. In severe cases, withdrawal of ciclesonide

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should be considered.
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, glaucoma (see also section 4.4).
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

4.9 Overdose:

Tiotropium bromide

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 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.
Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.

Formoterol fumarate

There is limited clinical experience on the management of overdose. An overdosage of formoterol fumarate would be likely to lead to effects that are typical of β_2-adrenergic agonists: headache, tremor, palpitations. Symptoms reported from isolated cases are tachycardia, prolonged QTc interval, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia, nausea, vomiting and somnolence.
Treatment of Overdose
Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective β-adrenergic blockers may be considered, but only subject to extreme caution since the use of β-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

Ciclesonide

Acute:
Inhalation by healthy volunteers of a single dose of 2880 micrograms 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.
Chronic:
After prolonged administration of 1280 micrograms 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.

5. PHARMACOLOGICAL PROPERTIES:
This Inhaler contains tiotropium bromide, formoterol fumarate and ciclesonide.

5.1 Pharmacodynamic properties:

Tiotropium bromide

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics
ATC code: R03B B04
Mechanism of action
Tiotropium bromide is a long-acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly antagonises the M_1 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. The long duration is probably due to the very slow dissociation from the M_1 receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.
Pharmacodynamic effects
The bronchodilation is primarily a local effect (on the airways), not a systemic one. Dissociation from M_3-receptors is faster than from M_2, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M_1 over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.
Cardiac electrophysiology
Electrophysiology: In a dedicated QT study involving 53 healthy volunteers, tiotropium bromide 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.
Clinical efficacy and safety
The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both, salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnoea, exacerbations and health-related quality of life.
Lung function
Tiotropium bromide, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings. The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance.
A randomised, placebo-controlled clinical study in 105 COPD patients demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether the drug was administered in the morning or in the evening.
Long-term clinical trials (6 months and 1 year)
Dyspnoea: Exercise tolerance
Tiotropium bromide significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index.). This improvement was maintained throughout the treatment period.
The impact of improvements in dyspnoea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with tiotropium bromide significantly improved symptom-limited exercise endurance time during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A) and 28.3% (Trial B) compared with placebo.
Health-related Quality of Life
In a 9-month, randomized, double-blind, placebo-controlled clinical trial of 492 patients, tiotropium bromide improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with tiotropium bromide which achieved a meaningful improvement in the SGRQ total score (i.e. > 4 units) was 10.9% higher compared with placebo (59.1% in the tiotropium bromide groups vs. 48.2% in the placebo group (p=0.029). The mean difference between the groups was 4.19 units (p=0.001; confidence interval: 1.69 – 6.68). The improvements of the subdomains of the SGRQ-score were 8.19 units for "symptoms", 3.91 units for "activity" and 3.61 units for "impact on daily life". The improvements of all of these separate subdomains were statistically significant.
COPD Exacerbations
In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).
A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of tiotropium bromide once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.
Table 1: Summary of exacerbation endpoints

Endpoint	tiotropium bromide 18 microgram (HandiHaler) N = 3,707	Salmeterol 50 microgram (HFA pMDI) N = 3,669	Ratio (95% CI)	p-value
Time [days] to first exacerbation†	187	145	0.83 (0.77 - 0.90)	<0.001
Time to first severe (hospitalised) exacerbation§	-	-	0.72 (0.61 - 0.85)	<0.001
Patients with ≥1 exacerbation, n (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85 - 0.95)	<0.001
Patients with ≥1 severe (hospitalised) exacerbation, n (%)*	262 (7.1)	336 (9.2)	0.77 (0.66 - 0.89)	<0.001

† Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.
* Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.
Compared with salmeterol, tiotropium bromide increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). Tiotropium bromide also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).
Long-term clinical trials (more than 1 year, up to 4 years)
In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3,006 receiving placebo and 2,987 receiving tiotropium bromide), the improvement in FEV_1 resulting from tiotropium bromide, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the tiotropium bromide group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV_1 compared to placebo was similar between tiotropium bromide and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).
Tiotropium active-controlled study
A long-term, large scale randomised, double-blind, active-controlled study with an observation period up to 3 years has been performed to compare the efficacy and safety of tiotropium bromide HandiHaler and tiotropium bromide Respimat (5,694 patients receiving tiotropium bromide HandiHaler; 5,711 patients receiving tiotropium bromide Respimat). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).
The time to first COPD exacerbation was numerically similar during the study with tiotropium bromide HandiHaler and tiotropium bromide Respimat (hazard ratio (tiotropium bromide HandiHaler/ tiotropium bromide Respimat) 1.02 with a 95% CI of 0.97 to 1.08). The median number of days to the first COPD exacerbation was 719 days for tiotropium bromide HandiHaler and 756 days for tiotropium bromide Respimat.
The bronchodilator effect of tiotropium bromide HandiHaler was sustained over 120 weeks, and was similar to tiotropium bromide Respimat. The mean difference in trough FEV_1 for tiotropium bromide Handi Haler versus tiotropium bromide Respimat was 0.010 L (95% CI -0.018 to 0.038 L).
In the post-marketing TioSpir study comparing tiotropium bromide Respimat and tiotropium bromide HandiHaler, all-cause mortality including vital status follow up was similar during the study with tiotropium bromide HandiHaler and tiotropium bromide Respimat (hazard ratio (tiotropium bromide HandiHaler/ tiotropium bromide Respimat) 1.04 with a 95% CI of 0.91 to 1.19).
Paediatric population
The European Medicines Agency has waived the obligation to submit results of studies with tiotropium bromide in all subsets of the paediatric population in COPD and cystic fibrosis.

Formoterol fumarate

Pharmacotherapeutic group: Adrenergics, inhalants; selective β2-adrenoreceptor agonists ATC-code: R03 AC13
Formoterol is a predominantly selective β_2-stimulator. Formoterol has bronchodilator activity in patients with reversible obstructive airway diseases. The onset of action is observed within one to three minutes. Significant bronchodilation is still present 12 hours after inhalation.
In humans formoterol is effective in the prophylaxis of bronchospasm induced by methacoline challenge.

Ciclesonide

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, Inhalants, Glucocorticoids, ATC Code: R03B A08
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.
In four clinical trials, ciclesonide has been shown to reduce airway hyper responsiveness to adenosine monophosphate in hyperreactive patients with maximal effect observed at the dose of 640 micrograms. In another trial, pretreatment with ciclesonide for seven days significantly attenuated the early and late phase reactions following inhaled allergen challenge. Inhaled ciclesonide treatment was also shown to attenuate the increase in inflammatory cells (total eosinophils) and inflammatory mediators in induced sputum.
A controlled study compared 24-hour plasma cortisol AUC in 26 adult asthmatic patients following 7 days of treatment. Compared to placebo, treatment with ciclesonide 320, 640, and 1,280 micrograms/day did not statistically significantly lower the 24-hour time averages of plasma cortisol (AUC_{0-24}, 24 hours) nor was a dose-dependent effect seen.
In a clinical trial involving 164 adult male and female asthmatic patients, ciclesonide was given at doses of 320 micrograms or 640 micrograms/day over 12 weeks. After stimulation with 1 and 250 micrograms cosyntropin, no significant changes in plasma cortisol levels were observed versus placebo.
Double-blind placebo-controlled trials of 12-weeks duration in adults and adolescents have shown that treatment with ciclesonide resulted in improved lung function as measured by FEV_1 and peak expiratory flow, improved asthma symptom control, and decreased need for inhaled beta-2 agonist.
In a 12-week study of 680 severe asthmatics, previously treated with 500-1,000 micrograms fluticasone propionate per day or equivalent, 87.3% and 93.3% of patients remained exacerbation-free during treatment with 160 or 640 micrograms of ciclesonide, respectively. At the end of the 12 week study period, the results showed a statistically significant difference between the doses of 160 micrograms and 640 micrograms/day ciclesonide with regard to the occurrence of an exacerbation after the first day of the study: 43 patients/339 (= 12.7%) in the 160 microgram/day group and 23 patients/341 (6.7%) in the 640 microgram/day group (Hazard ratio=0.526; p= 0.0134). Both ciclesonide doses resulted in comparable FEV_1 values at 12 weeks. Treatment-related adverse events were seen in 3.8% and 5% of patients treated with 160 or 640 micrograms per day of ciclesonide respectively. No study was performed to compare 160 micrograms, 320 micrograms and 640 micrograms daily dose in patients with severe asthma.

5.2 Pharmacokinetic properties:

Tiotropium bromide

Absorption: Following inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.
At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multicompartmental manner. Steady state trough plasma concentrations were 1.71 pg/ml.
Distribution: Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. 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 relevant extent.
Biotransformation: 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 tiotropium bromide is nonenzymatically 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 h in COPD patients. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3 µg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.
Linearity / Nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.
a) Characteristics in Patients
Geriatric Patients: As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients ≥ 65 years) This did not result in a corresponding increase in AUC0-6,ss or $C_{max,ss}$ values.
Renally Impaired Patients: Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CLCR 50-80 ml/min) resulted in slightly higher AUC0-6,ss (between 1.8-30% higher) and similar C_{max} ss values compared to patients with normal renal function(CLCR >80 ml/min).
In COPD patients with moderate to severe renal impairment (CLCR <50 ml/min), the intravenous administration of tiotropium resulted in doubling of the total exposure (82% higher AUC0-4h) and 52% higher Cmax) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after inhalation.
Hepatically Impaired Patients: Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.
Japanese COPD Patients: In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.
b) Pharmacokinetic / Pharmacodynamic Relationship(s)
There is no direct relationship between pharmacokinetics and pharmacodynamics.

Formoterol fumarate

Absorption and distribution
Following inhalation, formoterol is absorbed both from the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with a metered dose inhaler (MDI) may range between 60% and 90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hours after oral administration. Plasma protein binding of formoterol is 61-64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2-3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 µg of formoterol fumarate.
Biotransformation
Formoterol is widely metabolised and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. Cytochrome P450 isoenzymes CYP2D6, CYP2C19 and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.
Elimination
The cumulative urinary excretion of formoterol after single inhalation from inhaler increased linearly in the 12 – 96 µg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. 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.
After oral administration (40 to 80 µg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.
A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 ml/min.
Special populations
Hepatic/Renal impairment: the pharmacokinetics of formoterol has not been studied in patients with hepatic or renal impairment however, as formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis.

Ciclesonide

Ciclesonide is presented in HFA-134a propellant and ethanol as a solution aerosol, which demonstrates a linear relationship between different doses, puff strengths and systemic exposure.
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 γ-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/h/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.
Excretion:
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.
Pharmacokinetic characteristics in patients:
Asthmatic patients
Ciclesonide shows no pharmacokinetic changes in mild asthmatic patients compared to healthy subjects.
Elderly
According to population pharmacokinetics, age has no impact on the systemic exposure of the active metabolite.
Renal or hepatic impairment
Reduced liver function may affect the elimination of corticosteroids. In a study including patients with hepatic impairment suffering from liver cirrhosis, a higher systemic exposure to the active metabolite was observed.
Due to the lack of renal excretion of the active metabolite, studies on renal impaired patients have not been performed.

5.3 Preclinical safety data:

Tiotropium bromide

Many effects observed in conventional studies of safety pharmacology, repeat-dose toxicity, and reproductive toxicity could be explained by the anticholinergic properties of tiotropium bromide. Typically in animals reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy of the respiratory tract in rats and mice evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder in rats.
In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key developmental parameters, tracheal or key organ development were seen.
Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.
The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity was observed at local or systemic exposures more than five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

Formoterol fumarate

The effects of formoterol in rats and dogs were largely confined to the cardiovascular system and consisted of known pharmacological manifestations of high β_2-agonist doses.
A somewhat reduced fertility in male rats was observed at very high systemic exposure of formoterol.
No genotoxic effects of formoterol have been observed in in-vitro or in-vivo tests. In rats and mice, a slight increase in the incidence of benign uterine leiomyomas has been observed. This effect is looked upon as a class effect in rodents after long exposure to high doses of β_2-agonists.

Ciclesonide

Preclinical data with ciclesonide reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential.
In animal studies on reproductive toxicity, glucocorticosteroids have been shown to induce malformations (cleft palate, skeletal malformations). However, these animal results do not seem to be relevant for humans given recommended doses.
A treatment-related effect on the ovaries (namely atrophy) was observed at the top dose in two 12-month studies in dogs. This effect occurred at systemic exposures 5.27-8.34 times those noted at the 160 µg daily dose. The relevance of this finding to humans is unknown.
Animal studies with other glucocorticoids indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour. The relevance of these data to humans administered ciclesonide by inhalation is unknown.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients
Propellant HFA 227

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store between 15°-25°C. Do not freeze

6.5 Nature and contents of container
Carton of aerosol of 200 MD.

6.6 Instructions for use, handling and disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHORISATION NUMBER (S)
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10. DATE OF REVISION OF THE TEXT:
February 2015

Cipla

21051659

BEFORE USING YOUR TRIOHALE-T INHALER FOR THE FIRST TIME

A. Remove the cap from the mouthpiece & make sure that the mouthpiece is clean.

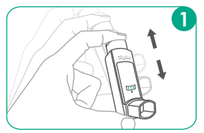
B. Hold the inhaler away from your face. Shake it well & release two puffs into the air.

C. Your **TRIOHALE-T** inhaler is now ready for use.

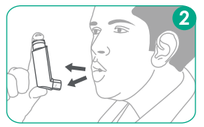
IF you have not used your inhaler for a week or more, shake well and release one puff into the air.

USING YOUR TRIOHALE-T INHALER

1. Sit or stand upright. Remove the mouthpiece cap & shake the inhaler well. Hold it upright as shown, with your thumb at the base below the mouthpiece. Place either one or two fingers on top of the canister.



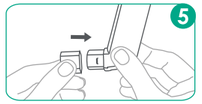
2. Breathe out fully, through your mouth.



3. Place the mouthpiece of the inhaler in your mouth between your teeth & close your lips around it (do not bite it). **Start breathing in slowly through your mouth. Press down the canister firmly & fully to release one spray while continuing to breathe in slowly & deeply.**

4. Remove the inhaler from your mouth & hold your breath for 10 seconds, or for as long as is comfortable. Breathe out normally.

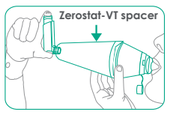
5. If another puff is required, wait for at least 1 minute. Shake inhaler well & repeat steps 2 to 4. After use, replace the mouthpiece cap firmly & snap it into position.



6. After taking each dose, rinse your mouth with water & spit it out.

IMPORTANT:
Do not rush steps 2, 3 & 4. It is important that you start to breathe in slowly before releasing a puff.
To ensure correct use of the inhaler, use it in front of a mirror for the first few times. If you see 'mist' coming out from the top of the inhaler or the sides of your mouth, start again from step 1. This escaping mist indicates incorrect technique.

In case of difficulty in using the inhaler correctly, you may use it along with a Zerostat-VT spacer.

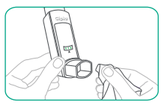


CLEANING YOUR TRIOHALE-T INHALER

It is important to keep your inhaler clean. Clean your inhaler atleast once a week.

1. Take the mouthpiece cap off. **DO NOT take the metal canister out of the actuator.**

2. Wipe the inside & the outside of the mouthpiece with a clean, dry cloth.



3. Replace the mouthpiece cap.

4. DO NOT wash or soak any part of the inhaler in water.

STORING YOUR TRIOHALE-T INHALER

Store between 15-25°C.
Do not freeze.

Keep the inhaler in an upright position, with the mouthpiece down.

DO NOT

× *Spray the inhaler in your eyes.*
× *Exceed the recommended dose.*
× *Change/tamper with the numbers on the dose indicator.*
× *Puncture or burn the inhaler even when empty as it is pressurized.*

Keep the inhaler out of the reach of children.

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