

## **Oxis Turbuhaler 4.5 µg/dose and 9 µg/dose**

*formoterol fumarate dihydrate*

**Inhalation powder**

### **Composition**

Each delivered dose (i.e. the dose leaving the mouthpiece) from Oxis Turbuhaler contains 4.5 or 9 micrograms formoterol fumarate dihydrate which is derived from a metered dose of 6 or 12 micrograms.

Excipient: Lactose monohydrate 450 micrograms per delivered dose (corresponding to 600 micrograms per metered dose)

### **Pharmaceutical form**

Inhalation powder. White powder.

### **Therapeutic indication**

Oxis Turbuhaler is indicated, as add on therapy to maintenance treatment with inhaled corticosteroids, for the relief of broncho-obstructive symptoms and prevention of exercise-induced symptoms in patients with asthma when adequate treatment with corticosteroids is not sufficient. Oxis Turbuhaler is also indicated for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD).

### **Posology and method of administration**

Use of doses above those normally required by the individual patient on more than 2 days per week is a sign of suboptimal disease control and maintenance treatment should be reassessed.

Oxis Turbuhaler is not recommended for use in children below 6 years due to insufficient data on safety and efficacy.

#### **4.5 µg/dose**

##### ***Asthma:***

In asthma, Oxis Turbuhaler can be used once or twice daily ('regular dosage'), and as 'relief medication' to relieve acute broncho-obstructive symptoms.

*Adults aged > 18 years:*

*Relief medication:* 1 or 2 inhalations for the relief of acute broncho-obstructive symptoms.

*Regular dosage:* 1 or 2 inhalations once or twice daily.

Some patients may need 4 inhalations once or twice daily.

*Prevention of exercise-induced bronchoconstriction:* 2 inhalations before exercise.

The daily dose for regular use should not exceed 8 inhalations, however occasionally up to a maximum of 12 inhalations may be allowed within a 24-hour period. No more than 6 inhalations should be taken on any single occasion.

*Children and adolescents, 6 years and older:*

*Relief medication:* 1 or 2 inhalations for the relief of acute broncho-obstructive symptoms.

*Regular dosage:* 2 inhalations once or twice daily.

*Prevention of exercise-induced bronchoconstriction:* 1 or 2 inhalation before exercise.

The regular daily dose should not exceed 4 inhalations, however occasionally up to a maximum of 8 inhalations may be allowed within a 24-hour period. No more than 2 inhalations should be taken on any single occasion.

### ***COPD:***

*Regular dosage:* 2 inhalations once or twice daily.

The daily dose for regular use should not exceed 4 inhalations. If required, additional inhalations above those prescribed for regular therapy may be used for relief of symptoms, up to a maximum total daily dose of 8 inhalations, (regular plus as required). No more than 4 inhalations should be taken on any single occasion.

### **9 µg/dose**

#### ***Asthma:***

In asthma, Oxis Turbuhaler can be used once or twice daily ('regular dosage'), and as 'relief medication' to relieve acute broncho-obstructive symptoms.

*Adults aged > 18 years:*

*Relief medication:* 1 inhalation for the relief of acute broncho-obstructive symptoms.

*Regular dosage:* 1 inhalation once or twice daily. Some patients may need 2 inhalations once or twice daily.

*Prevention of exercise-induced bronchoconstriction:* 1 inhalation before exercise.

The daily dose for regular use should not exceed 4 inhalations, however occasionally up to a maximum of 6 inhalations may be allowed within a 24-hour period. No more than 3 inhalations should be taken on any single occasion.

*Children and adolescents, 6 years and older:*

*Relief medication:* 1 inhalation for the relief of acute broncho-obstructive symptoms.

*Regular dosage:* 1 inhalation once or twice daily.

*Prevention of exercise-induced bronchoconstriction:* 1 inhalation before exercise.

The regular daily dose should not exceed 2 inhalations, however occasionally up to a maximum of 4 inhalations may be allowed within a 24-hour period. No more than 1 inhalation should be taken on any single occasion.

***COPD:***

*Regular dosage:* 1 inhalation once or twice daily.

The daily dose for regular use should not exceed 2 inhalations.

If required, additional inhalations above those prescribed for regular therapy may be used for relief of symptoms, up to a maximum total daily dose of 4 inhalations, (regular plus as required). No more than 2 inhalations should be taken on any single occasion.

*Special patient groups:* There are no special dosing requirements for elderly patients. There are no data available for use of Oxis Turbuhaler in patients with hepatic or renal impairment.

Oxis Turbuhaler is inspiratory flow driven which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

*Note!* It is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is obtained.

It is important to instruct the patient never to chew or bite on the mouthpiece and never to use the inhaler if it has been damaged or if the mouthpiece has become detached.

The patient may not taste or feel any medication when using Oxis Turbuhaler due to the small amount of drug dispensed.

**Contraindications**

Hypersensitivity to formoterol or to lactose (which contains small amounts of milk proteins).

**Special Warnings and Precautions for Use**

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

Asthmatic patients who require therapy with long-acting  $\beta_2$ -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 Oxis Turbuhaler even when symptoms decrease. Should symptoms persist, or treatment with  $\beta_2$ -agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy.

Although Oxis Turbuhaler may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Oxis Turbuhaler 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 Oxis Turbuhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Oxis Turbuhaler. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Oxis Turbuhaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Oxis Turbuhaler should be used.

The maximum daily dose should not be exceeded. The long term safety of regular treatment at higher doses than 36 micrograms per day in adults with asthma, 18 micrograms per day in children with asthma and 18 micrograms per day in patients with COPD has not been established.

Frequent need of medication (i.e. prophylactic treatment eg corticosteroids and long acting  $\beta_2$ -agonists) for the prevention of exercise-induced bronchoconstriction several times every week, despite an adequate maintenance treatment, can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of the compliance.

Caution should be observed when treating patients with 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.

Formoterol may induce prolongation of the QTc-interval. Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval (see Interactions).

Due to the hyperglycaemic effects of  $\beta_2$ -agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from  $\beta_2$ -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.

As with other inhalation therapy, the potential for paradoxial bronchospasm should be considered.

Oxis Turbuhaler contains lactose 450 micrograms per delivered dose (corresponding to 600 micrograms per metered dose). This amount does not normally cause problems in lactose intolerant people. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Children up to the age of 6 years should not be treated with Oxis Turbuhaler, as no sufficient experience is available for this group.

## **Interactions**

No specific interaction studies have been carried out with Oxis Turbuhaler.

Concomitant treatment with other sympathomimetic substances such as other  $\beta_2$ -agonists or ephedrine may potentiate the undesirable effects of Oxis Turbuhaler and may require titration of the dose.

Concomitant treatment with xanthine derivatives, steroids or diuretics such as thiazides and loop diuretics may potentiate a rare hypokalaemic adverse effect of  $\beta_2$ -agonists.

Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

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.

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

Beta-adrenergic blockers can weaken or inhibit the effect of Oxis Turbuhaler. Oxis Turbuhaler should therefore not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons.

## **Pregnancy and lactation**

There are no adequate data from the use of formoterol in pregnant women. In animal studies formoterol has caused implantation losses as well as decreased early postnatal survival and birth weight. The effects appeared at considerably higher systemic exposures than those reached during clinical use of Oxis Turbuhaler. Treatment with Oxis Turbuhaler may be considered at all stages of pregnancy if needed to obtain asthma control, and if the expected benefit to the mother is greater than any possible risk to the foetus. The potential risk for human is unknown.

It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of Oxis Turbuhaler 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.

### Effects on the ability to drive and use machines

Oxis Turbuhaler has no influence on the ability to drive and use machines.

### Undesirable effects

The most commonly reported adverse events of  $\beta_2$ -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 given below, listed by system organ class and frequency. Frequency are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ) and  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$  and  $< 1/100$ ), rare ( $\geq 1/10\ 000$  and  $< 1/1000$ ) and very rare  $< 1/10\ 000$ ).

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris
Gastrointestinal disorders	Rare	Nausea
Immune system disorders	Rare	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus
Investigations	Very rare	Prolongation of QTc-interval
Metabolic and nutrition disorders	Rare	Hypokalemia/Hyperkalemia
	Very rare	Hyperglycemia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Muscle cramps

Nervous system disorders	Common	Headache, tremor
	Very rare	Taste disturbances, dizziness
Psychiatric disorders	Uncommon	Agitation, restlessness, sleep disturbances
Vascular disorders	Very rare	Variations in blood pressure

As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases.

Treatment with  $\beta_2$ -agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

The excipient lactose contains small amounts of milk proteins. These may cause allergic reactions.

### **Overdose**

There is limited clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of  $\beta_2$ -agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment is indicated.

Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the use of  $\beta$ -adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

### **Pharmacodynamic properties**

Formoterol is a selective  $\beta_2$ -adrenoceptor agonist that produces relaxation of bronchial smooth muscle. Formoterol thus has a bronchodilating effect in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation and has a mean duration of 12 hours after a single dose.

### **Pharmacokinetic properties**

#### **Absorption**

Inhaled formoterol is rapidly absorbed. Peak plasma concentration is reached about 10 minutes after inhalation.

In studies the mean lung deposition of formoterol after inhalation via Turbuhaler ranged from 28-49% of the delivered dose (corresponding to 21-37% of the metered dose). The total systemic availability for the higher lung deposition was around 61% of the delivered dose (corresponding to 46% of the metered dose).

**Distribution and metabolism**

Plasma protein binding is approximately 50%.

Formoterol is metabolised via direct glucuronidation and O-demethylation. The enzyme responsible for O-demethylation has not been identified. Total plasma clearance and volume of distribution has not been determined.

**Elimination**

The major part of the dose of formoterol is eliminated via metabolism. After inhalation 8-13% of the delivered dose (corresponding to 6-10% of the metered dose) of formoterol is excreted unmetabolised in the urine. About 20% of an intravenous dose is excreted unchanged in the urine. The terminal half-life after inhalation is estimated to be 17 hours.

*Special populations:*

The effect of decreased liver or kidney function on the pharmacokinetics of formoterol and the pharmacokinetics in the elderly is not known. As formoterol is primarily eliminated via liver metabolism an increased exposure can be expected in patients with severe liver cirrhosis.

**List of excipients**

Lactose monohydrate (which contains milk proteins).

**Incompatibilities**

Not applicable

**Shelf life**

Please see outer pack.

**Special precautions for storage**

Do not store above 30°C.

Keep the container/cap tightly closed.

**Pack size**

Please see outer carton for pack size.

**Date of revision of text**

15 January 2008

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## **Oxis Turbuhaler 4.5 µg/dose and 9 µg/dose**

*formoterol fumarate dihydrate*

### **Inhalation powder**

Pictures will be included in printed leaflet

### **How to use Oxis Turbuhaler**

Turbuhaler is a multidose inhaler from which very small amounts of powder are administered. When you breathe in through Turbuhaler the powder is delivered to the lungs. It is therefore important that you inhale forcefully and deeply through the mouthpiece.

Turbuhaler is very easy to use. Simply follow the instructions below.

- 1        Unscrew and lift off the cover.
- 2        Hold the inhaler upright with the grip downwards. Load the inhaler with a dose by turning the grip as far as it will go and then back to the original position.
- 3        Breathe out. Do not breathe out through the inhaler.
- 4        Place the mouthpiece gently between your teeth, close your lips and breathe in forcefully and deeply through your mouth. Do not chew or bite on the mouthpiece. Do not use Turbuhaler if it has been damaged or if the mouthpiece has become detached.
- 5        Before breathing out, remove the inhaler from your mouth.  
  
          If more than one dose has been prescribed, repeat steps 2-5.
- 6        Replace the cover.

#### **NOTE!**

Never breathe out through the mouthpiece.

Always replace the cover properly after use.

As the amount of the powder dispensed is very small, you may not be able to taste it after inhalation. However, you can still be confident that the dose has been inhaled if you have followed the instructions.

## **Cleaning**

Clean the outside of the mouthpiece regularly (weekly) with a dry tissue.

Do not use water for cleaning the mouthpiece.

## **Dose indicator**

When a red mark is first seen in the indicator window there are approximately 20 doses left. When the red mark has reached the lower edge of the window the inhaler will no longer deliver the correct amount of medicine, and should be discarded. The sound heard as you shake the inhaler is not produced by the medication but by a drying agent.

## **Disposal**

Always be sure to dispose of your used Turbuhaler responsibly/in the recommended way, since some of the medicine will remain inside it.