Compliance
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.

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.

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 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 6 inhalations may be allowed within a 24-hour period. No more than 6 inhalations should be taken on any single occasion.
Warnings and precautions for use

Asthmatic patients who require therapy with long-acting β2-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 β2-agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy. Oxis Turbuhaler should not be initiated to treat a severe asthma exacerbation. 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 for the prevention of exercise-induced bronchoconstriction can be a sign of suboptimal asthma control, and warrants a reassessment of the asthma therapy and an evaluation of the compliance. If the patient needs prophylactic treatment for exercise induced bronchoconstriction several times every week despite an adequate maintenance treatment (e.g. corticosteroids and long-acting β2-agonists), the total asthma management should be reassessed by a specialist.

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 β2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients. Potentially serious hypokalaemia may result from β2-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 paradoxical 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.

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

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 metabolism an increased exposure can be expected in patients with severe liver cirrhosis.

**Interaction**

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

Concomitant treatment with other sympathomimetic substances such as other β2-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 β2-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**

Clinical experience in pregnant women is limited. 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.

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 does not affect the ability to drive or use machines.

**Undesirable effects**

The most commonly reported adverse events of β2-agonist therapy, such as tremor and palpitations, tend to be mild and disappear within a few days of treatment.

<table>
<thead>
<tr>
<th>Common 1% to 10%</th>
<th>Cardiac disorders: Palpitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders: Headache, tremor</td>
<td></td>
</tr>
<tr>
<td>Uncommon 0.1% to 1%</td>
<td>Cardiac disorders: Tachycardia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders: Muscle cramps</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders: Agitation, restlessness, sleep disturbance</td>
<td></td>
</tr>
<tr>
<td>Rare 0.01% to 0.1%</td>
<td>Cardiac disorders: Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles</td>
</tr>
<tr>
<td>Gastrointestinal disorders: Nausea</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders: Hypersensitivity reactions, e.g. bronchospasm, exanthena, urticaria, pruritus</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders: Hypokalaemia/hyperkalaemia</td>
<td></td>
</tr>
</tbody>
</table>
As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases. Treatment with β2-agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

**Overdose**

There is limited clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of β2-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 β-adrenergic blocker medication may provoke bronchospasm. Serum potassium should be monitored.

**Pharmacodynamic properties**

Formoterol is a selective β2-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.

**List of excipients**

Lactose monohydrate.

**Incompatibilities**

Not applicable.

**Shelf life**

Please see outer pack.

**Special precautions for storage**

Do not store above 30°C.

Should be stored with cover tightened.

**Pack size**

Please see outer carton for pack size.

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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.