Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxis Turbohaler 12, inhalation powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Lactose monohydrate 891 micrograms per delivered dose. See section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder.
White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oxis Turbohaler is indicated in adults, adolescents and children aged 6 years and older, 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 Turbohaler is also indicated in adults for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology
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 Turbohaler 6:

Asthma:
In asthma, Oxis Turbohaler 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 inhalations 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:
Adults aged > 18 years:
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). More than 4 inhalations should not be taken on any single occasion.

Special populations:
Elderly
There are no special dosing requirements for elderly patients.

Patients with hepatic or renal impairment:
There are no data available for use of Oxis Turbohaler in patients with hepatic or renal impairment (see also section 5.2).

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

NB! A higher strength (12 micrograms/dose) is available as an alternative for patients requiring 2 or more inhalations

Oxis Turbohaler 12:

Asthma:
In asthma, Oxis Turbohaler 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:
Adults aged > 18 years
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 2 inhalations (regular plus as required). More than 2 inhalations should not be taken on any single occasion.

Special population:
Elderly
There are no special dosing requirements for elderly patients.

Patients with hepatic and renal impairment:
There are no data available for use of Oxis Turbohaler in patients with hepatic or renal impairment (see also section 5.2).

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

NB! A lower strength (6 micrograms/dose) is also available.

Method of administration
Instruction for correct use of Oxis Turbohaler
Oxis Turbohaler 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 Turbohaler due to the small amount of drug dispensed.

Detailed instructions for use are packed together with each inhaler.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Asthmatic patients who require therapy with long acting b_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 Turbohaler even when symptoms decrease. Should symptoms persist, or treatment with b_2-agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the maintenance therapy.

Although Oxis Turbohaler 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 Turbohaler 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 Turbohaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Oxis Turbohaler. Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Oxis Turbohaler. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Oxis Turbohaler 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 e.g. corticosteroids and long-acting b_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.

Cardiovascular and endocrine disorders
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.

QTc prolongation
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 section 4.5).

Diabetic patients
Due to the hyperglycaemic effects of b_2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Hypokalaemia
Potentially serious hypokalaemia may result from b_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.

Bronchospasm
As with other 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).

Lactose intolerance
Oxis Turbohaler 12 contains lactose 891 micrograms per delivered dose. These amounts do 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.

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

4.5 Interaction with other medicinal products and other forms of interactions

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

Concomitant treatment with other sympathomimetic substances such as other b_2-agonists or ephedrine may potentiate the undesirable effects of Oxis Turbohaler 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 b_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.

The bronchodilating effects of formoterol can be enhanced by anticholinergic drugs.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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 Turbohaler. Treatment with Oxis Turbohaler 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 humans is unknown.

Breast-feeding

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 Turbohaler 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
Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at considerably higher systemic exposures than those reached during clinical use. Thus, these animal experimental results do not seem to be relevant in humans.

4.7 Effects on ability to drive and use machines

Oxis Turbohaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse events of b_2-agonist therapy, such as tremor and palpitations, tend to be mild and disappear within a few days of treatment.

Tabulated list of adverse reactions
Adverse reactions, which have been associated with formoterol are given below, listed by system organ class and frequency. Frequency are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1 000 and <1/100), rare (≥1/10 000 and <1/1000) and very rare <1/10 000).

System Organ Class	Frequency	Adverse Reaction
Cardiac disorders	Uncommon	Palpitations
	Uncommon	Tachycardia
	Uncommon	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles.
	Uncommon	Angina pectoris
	Very rare	Prolongation of QTc interval
Gastrointestinal disorders	Common	Nausea
Immune system disorders	Uncommon	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus
Metabolic and nutrition disorders	Uncommon	Hypokalaemia
	Uncommon	Hyperglycaemia
Musculoskeletal, connective tissue and bone disorders	Common	Muscle cramps
Nervous system disorders	Common	Headache*, tremor, dizziness
	Uncommon	Taste disturbances
Psychiatric disorders	Uncommon	Sleep disturbances
	Rare	Agitation, restlessness
Vascular disorders	Uncommon	Variations in blood pressure

* Headache occurred in 6.5% of patients in OXIS and 6.2% on placebo.

Description of selected adverse reactions
As with all inhalation therapy, paradoxical bronchospasm may occur in very rare cases (see section 4.4).
Treatment with b_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.

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. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace

IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: http://www.hpra.ie/
e-mail: medsafety@hpra.ie

4.9 Overdose

There is limited clinical experience on the management of overdose.

Symptoms
An overdose would likely lead to effects that are typical of b_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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective β_2-agonist, formoterol, ATC code: R03A C13.

Mechanism of action and pharmacodynamic effects
Formoterol is a selective b_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.

5.2 Pharmacokinetic properties

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

In a pharmacokinetic study, the mean lung deposition of formoterol after inhalation via Turbohaler was 43% of the delivered dose. The total systemic availability was around 60% of the delivered dose.

Distribution and biotransformation
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.

Elimination
The major part of the dose of formoterol is eliminated via metabolism. Total plasma clearance and volume of distribution has not been determined.

After inhalation 8-13% of the delivered 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.

Linearity/non-linearity
Systemic exposure for formoterol correlates in a linear fashion to administered dose.

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.

5.3 Preclinical safety data

The effects of formoterol seen in toxicity studies in rats and dogs were mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological manifestations seen after the administration of high doses of b_2-agonists.
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 observed in rodents after long exposure to high doses of b_2-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Keep the container/cap tightly closed.

6.5 Nature and contents of container

Oxis Turbohaler is a multidose, inspiratory flow driven, dry powder inhaler. The inhaler is made of plastic parts (PP, PC, HDPE, LDPE, LLDPE, PBT).
Each inhaler contains 60 doses.
Each pack contains either 60 doses (1 inhaler), 3x60 doses (3 inhalers), 10x60 doses (10 inhalers), 18x60 doses (18 inhalers) or 20x60 doses (20 inhalers).
Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1019/015/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2002
Date of last renewal: 10 March 2007

10 DATE OF REVISION OF THE TEXT

January 2019