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1 NAME OF THE MEDICINAL PRODUCT

OXIS® TURBUHALER® inhalation powder 4.5 micrograms/dose
OXIS® TURBUHALER® inhalation powder 9 micrograms/dose.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose delivers:
Active Ingredient
Formoterol fumarate dihydrate 4.5 micrograms or 9 micrograms.

The delivered dose of formoterol fumarate dihydrate from Oxis Turbuhaler, (i.e., the dose to the patient) is 4.5 micrograms and 9 micrograms, respectively for the two strengths. To reach the targeted delivered dose, the metered dose consists of about 0.6 mg powder mixture containing 6 micrograms and 12 micrograms respectively, of formoterol fumarate dihydrate.

Other Ingredient
Lactose monohydrate (which contains milk proteins).

3 PHARMACEUTICAL FORM

Inhalation powder.

White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxis Turbuhaler is indicated for the relief of broncho-obstructive symptoms and prevention of exercise-induced symptoms in asthmatics 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).

4.2 Posology and method of administration

The dosage of OXIS TURBUHALER should be individualised.

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

Relief of broncho-obstructive symptoms

Adults
Normal dosage: 4.5 - 9 micrograms once or twice daily. The dose can be administered in the morning and/or at night. Some patients may need 18 micrograms once or twice daily. A daily dose above 36 micrograms is not recommended.

If required, additional actuations above those prescribed for the regular maintenance therapy may be used for relief of symptoms up to a maximum total daily dose of 54 micrograms (maintenance plus as required). More than 27 micrograms should not be taken at any single occasion. However, frequent use, which is more than twice daily and/or more than 2 days per week, of doses above normal maintenance treatment is a sign of suboptimal asthma control and treatment should be reassessed.

Children 6 Years of Age and Older
Normal dosage: 4.5 - 9 micrograms once or twice daily. The dose can be administered in the morning and/or at night. A daily dose above 18 micrograms is not recommended.

Special patient groups:
No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment at the recommended normal doses (See also Special warnings and special precautions for use).

Chronic Obstructive Pulmonary Disease (COPD).

Adults
Normal dosage: 9 micrograms once or twice daily. The maximum daily dose for regular use is 18 micrograms.
If required, additional actuations above those prescribed for the regular maintenance therapy may be used for relief of symptoms up to a maximum total daily dose of 36 micrograms (maintenance plus as required). More than 18 micrograms should not be taken on any single occasion. However, frequent use, which is more than twice daily and/or more than 2 days per week, of doses above normal maintenance treatment is a sign of suboptimal control and treatment should be reassessed.

Prevention of exercise-induced bronchoconstriction (EIB)

Adults and children 6 years and older:
4.5 - 9 micrograms before exercise (see below: “Warnings”).

The maximum daily dose given for normal dosage should not be exceeded.

Instruction for correct use of Turbuhaler

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 carefully read the instructions for use in the patient information leaflet which are packed together with each inhaler
- to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- never to breathe out through the mouthpiece

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 Turbuhaler due to the small amount of drug dispensed.

4.3 Contraindications

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

4.4 Special warnings and special 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 β_2-agonists, should also receive optimal 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 β_2-agonists need to be increased, this indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy. 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 for the prevention of EIB 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 EIB several times every week despite an adequate maintenance treatment (e.g. corticosteroids and long-acting β_2-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.

Caution should be observed when treating patients with prolongation of the QTc-interval and in patients treated with drugs affecting the QTc-interval (see 4.5). Formoterol itself may induce prolongation of the QTc-interval.

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

Potentially serious hypokalemia 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 hypokalemic effect may be potentiated by concomitant treatment with xanthine-derivatives, steroids and diuretics (see Interactions). The serum potassium levels should therefore be monitored.

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

OXIS TURBUHALER contains lactose 450 micrograms/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.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been carried out with OXIS TURBUHALER.

Concomitant treatment with other sympathomimetic substances such as other β_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 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.

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

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.

4.6 Pregnancy and lactation

There are no adequate data from the use of formoterol in pregnant women. 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 fetus. The potential risk for human is unknown.

It is not known whether formoterol passes over to 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.

4.7 Effects on ability to drive and use machines

OXIS TURBUHALER does not affect the ability to drive or use machines.

4.8 Undesirable effects

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 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).

Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles.
	Very rare	Angina pectoris, Prolongation of QTc-interval
Gastrointestinal disorders	Rare	Nausea
Immune system disorders	Rare	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritus
Metabolic and nutrition disorders	Rare	Hypokalemia
	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 (see section 4.4.).

Treatment with β2-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.

4.9 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, arrythmia, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Formoterol is a selective β_2-adrenergic stimulant 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 and the 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 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.

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 administration of high doses of β_2-agonists.

A somewhat reduced fertility in male rats was observed at high systemic exposure to 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 observed in rodents after long exposure to high doses of β_2-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

See section 2

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store in a cool place (below 30°C).
Should be stored with cover tightened.

6.4 Presentation

Packs providing 60 inhalation doses.

6.5 Instructions for use, handling and disposal

See section 4.2.

7 REGISTRATION NUMBERS

OXIS 4.5 mcg/dose: 110 48 29179 00
OXIS 9 mcg/dose: 108 99 29180 00

7 MANUFACTURER

Teva Pharmaceutical Industries Ltd,
P.O.Box 3190, Petach-Tikva.