MINISTRY FOR SOCIAL POLICY
Strategy and Sustainability Division

MSP/HEC Circular No 3 /2008 26th March 2008
DH 1046/2008

Attention all: Consultants
Medical Practitioners
Pharmacists
Nurses

Re: Change-over of long acting Beta$_2$-agonists

Salmeterol 25mcg inhaler was previously available within the Government Health Services for patients suffering from asthma and respiratory failure.

Kindly note that Salmeterol 25mcg has been replaced by Formoterol 4.5mcg (Oxis® Turbohaler® 6) dry powder inhaler and Formoterol 12mcg (Atimos Modulite®) metered dose inhaler. Formoterol 4.5mcg (Oxis® Turbohaler® 6) is indicated for children over 6 years while formoterol 12mcg (Atimos Modulite®) is to be used in adults including elderly and adolescents aged over 12 years and older.

The 'off-license' form for use of the dry powder inhaler for children under 6 years of age has to be filled by the Consultant Paediatricians.

Kindly refer to the Summary of Product Characteristics (SPCs) for your reference and information.

For your attention please

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Annex 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxis Turbohaler 6, inhalation powder.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For a 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 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 for the relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease (COPD).

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

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 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). More than 4 inhalations should not 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 Turbohaler in patients with hepatic or renal impairment (see also section 5.2).

NB! A higher strength is available as an alternative for patients requiring 2 or more inhalations.

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

4.4 Special warnings and special precautions for use

Oxis Turbohaler 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 Oxis Turbohaler 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 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 β_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 4.5).

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

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.

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

Oxis Turbohaler 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 Turbohaler, 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 Turbohaler.

Concomitant treatment with other sympathomimetic substances such as other β_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 β_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 Turbohaler. Oxis Turbohaler 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. 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 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 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.

4.7 Effects on ability to drive and use machines

Oxis Turbohaler has no influence on the ability to drive and 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
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 β_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.

4.9 Overdose

There is limited clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of β_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 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-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 studies the mean lung deposition of formoterol after inhalation via Turbohaler 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.

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 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

Lactose monohydrate (which contains milk proteins).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.. 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 precaution for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with the local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited 600 Capability Green
Luton, LU13LU
UK

8. MARKETING AUTHORISATION NUMBER(S)

MA 010/00101

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

23 March 2006

10. DATE OF REVISION OF THE TEXT

23 November 2007