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MSOC/HEC Circular No 54/2008 27th June 2008

Attention all Consultants
Medical Officers
Pharmacists
Nurses

Re: Long acting Beta$_2$-agonists

Kindly note that Salmeterol 25mcg (Serevent®) metered dose inhaler, Formoterol 4.5mcg (Oxis® Turbohaler® 6) dry powder inhaler and Formoterol 12mcg (Atimos Modulite®) metered dose inhaler are available on the Government Formulary List. Salmeterol 25mcg will be reserved for children aged 4-5 years. Formoterol 4.5mcg (Oxis® Turbohaler® 6) is to be dispensed for children over 6 years while formoterol 12mcg (Atimos Modulite®) is to be dispensed in adults including elderly and adolescents aged over 12 years and older.

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

For your attention please

Ms. Isabelle Zahra Pulis
Director, Pharmaceutical Policy and Monitoring

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

Annex 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Serevent Evohaler 25 micrograms per actuation pressurised inhalation suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 25 micrograms salmeterol (as xinafoate). This is equivalent to a delivered dose (ex-actuator) of 21 micrograms salmeterol (as xinafoate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pressurised inhalation suspension.

White to off white suspension sealed in an aluminium canister in a green actuator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Regular symptomatic add-on treatment of reversible airways obstruction in patients with asthma, including those with nocturnal asthma, who are inadequately controlled on inhaled corticosteroids in accordance with current treatment guidelines. Treatment of chronic obstructive pulmonary disease (COPD). Prevention of exercise-induced asthma.

4.2 Posology and method of administration

Serevent Evohaler is for inhalation use only.

Serevent Evohaler should be used regularly. The full benefits of treatment will be apparent after several doses of the medicinal product. As there may be adverse reactions associated with excessive dosing with this class of medicinal product, the dosage or frequency of administration should only be increased on medical advice.

<u>Recommended Doses:</u>

Asthma
Adults and adolescents 12 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

In asthma patients with more severe airways obstruction up to four inhalations of 25 micrograms of salmeterol twice daily may be of benefit.

Children aged 4 years and older:

Two actuations of 25 micrograms salmeterol twice daily.

Children below 4 years of age:

Serevent Evohaler is not recommended for use in children below four years of age due to insufficient data on safety and efficacy.

COPD

Adults: Two actuations of 25 micrograms salmeterol twice daily.

Children: There is no relevant indication for use of Serevent Evohaler in children.

Special patient groups:

There is no need to adjust the dose in elderly patients or in those with renal impairment. There are no data available on the use of Serevent Evohaler in patients with hepatic impairment.

INSTRUCTIONS FOR USE:

Patients should be carefully instructed in the proper use of their inhaler (see Patient Information Leaflet).

1. Patients should remove the mouthpiece cover by gently squeezing the sides of the cover.

2. Patients should check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.

3. Patients should shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed. Before using for the first time or if the inhaler has not been used for a week patients should release one puff into the air to make sure that it works.

4. Patients should hold the inhaler upright between fingers and thumb with their thumb on the base, below the mouthpiece.

5. Patients should breathe out as far as is comfortable and then place the mouthpiece in their mouth between their teeth and close their lips around it. Patients should be instructed not to bite the mouthpiece.

6. Just after starting to breathe in through their mouth patients should press down on the top of the inhaler to release salmeterol while still breathing in steadily and deeply.

7. While holding their breath, patients should take the inhaler from their mouth and take their finger from the top of the inhaler. They should continue holding their breath for as long as is comfortable.

8. If patients are going to take a further puff, they should keep the inhaler upright and wait about half a minute before repeating steps 3 to7.

9. After use patients should always replace the mouthpiece cover to keep out dust and fluff.

10. Patients should replace the mouthpiece cover by firmly pushing and snapping the cap into position.

Important:

Patients should not rush stages5, 6 and 7. It is important that they start to breathe in as slowly as possible just before operating their inhaler.

Patients should practise in front of a mirror for the first few times. If they see "mist" coming from the top of their inhaler or the sides of their mouth they should start again from stage 2.

Serevent Evohaler should be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath which is often the case for children and the elderly.

Cleaning:

The inhaler should be cleaned at least once a week by:

1. Removing the mouthpiece cover.

2. Wiping the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue.

3. Replacing the mouthpiece cover.

The canister must not be removed from the plastic casing when cleaning the inhaler.

PATIENTS MUST NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

Serevent Evohaler is contraindicated in patients with hypersensitivity to salmeterol xinafoate or to the excipient (see Section 6.1).

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests.

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

Salmeterol is not a replacement for oral or inhaled corticosteroids. Its use is complementary to them. Patients must be warned not to stop steroid therapy and not to reduce it without medical advice even if they feel better on salmeterol.

Salmeterol should not be used to treat acute asthma symptoms for which a fast and short-acting inhaled bronchodilator is required. Patients should be advised to have their medicinal product to be used for the relief of acute asthma symptoms available at all times.

Increasing use of short-acting bronchodilators to relieve asthma symptoms indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or more inhalations than usual are required. In this situation the patient should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way.

Although Serevent may be introduced as add-on therapy when inhaled corticosteroids do not provide adequate control of asthma symptoms, patients should not be initiated on Serevent 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 Serevent. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Serevent.

Sudden and progressive deterioration in control of asthma is potentially life-threatening and the patient should undergo urgent medical assessment. Consideration should be given to increasing corticosteroid therapy. Under these circumstances daily peak flow monitoring may be advisable. For maintenance treatment of asthma salmeterol should be given in combination with inhaled or oral corticosteroids. Long-acting bronchodilators should not be the only or the main treatment in maintenance asthma therapy (see Section 4.1).

Once asthma symptoms are controlled, consideration may be given to gradually reducing the dose of Serevent. Regular review of patients as treatment is stepped down is important. The lowest effective dose of Serevent should be used.

Salmeterol should be administered with caution in patients with thyrotoxicosis.

There have been very rare reports of increases in blood glucose levels (see Section 4.8) and this should be considered when prescribing to patients with a history of diabetes mellitus.

Cardiovascular effects, such as increases in systolic blood pressure and heart rate, may occasionally be seen with all sympathomimetic drugs, especially at higher than therapeutic doses. For this reason, salmeterol should be used with caution in patients with pre-existing cardiovascular disease.

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

Data from a large clinical trial (the Salmeterol Multi-Center Asthma Research Trial, SMART) suggested African-American patients were at increased risk of serious respiratory-related events or deaths when using salmeterol compared with placebo (see section 5.1). It is not known if this was due to pharmacogenetic or other factors. Patients of black African or Afro-Caribbean ancestry should therefore be asked to continue treatment but to seek medical advice if asthma symptoms remained uncontrolled or worsen whilst using Serevent.

Patients should be instructed in the proper use of their inhaler and their technique checked to ensure optimum delivery of the inhaled medicinal product to the lungs.

As systemic absorption is largely through the lungs, the use of a spacer plus metered dose inhaler may vary the delivery to the lungs. It should be noted that this could potentially lead to an increase in the risk of systemic adverse effects so that dose adjustment may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Both non-selective and selective beta-blockers should be avoided in patients with asthma unless there are compelling reasons for their use.

Potentially serious hypokalaemia may result from β_2 agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics.

4.6 Pregnancy and lactation

There are insufficient data on the use of salmeterol or this medicinal product during pregnancy and lactation in women to assess the possible harmful effects. In animal studies fetal abnormalities occur after administration of beta-2-adrenoreceptor agonists (see Section 5.3).

Use of Serevent Evohaler during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

It is unknown whether salmeterol is excreted in human breast milk. Animal studies in rats have shown excretion of salmeterol in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Serevent Evohaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Serevent Evohaler therapy to the woman.

Studies of HFA-134a revealed no effects on the reproductive performance and lactation of adult or two successive generations of rats or on the fetal development of rats or rabbits.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Common and uncommon events were generally determined from clinical trial data. The incidence on placebo was not taken into account. Very rare events are generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard dose of 50mcg twice daily. Frequencies at the higher dose of 100mcg twice daily have also been taken to account where appropriate.

System Organ Class	***Adverse Reaction***	***Frequency***
Immune System Disorders	***Hypersensitivity reactions with the following manifestations:***	
	Rash (itching and redness)	***Uncommon***
	Anaphylactic reactions including oedema and angioedema, bronchospasm and anaphylactic shock	***Very Rare***
Metabolism & Nutrition Disorders	***Hypokalaemia***	***Rare***
	Hyperglycaemia	***Very Rare***
Psychiatric Disorders	***Nervousness***	***Uncommon***
	Insomnia	***Rare***
Nervous System Disorders	***Headache***	***Common***
	Tremor	***Common***
	Dizziness	***Rare***

System Organ Class	*Adverse Reaction*	*Frequency*
Cardiac Disorders	***Palpitations***	***Common***
	Tachycardia	***Uncommon***
	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).	***Very Rare***
Respiratory, Thoracic & Mediastinal Disorders	***Oropharyngeal irritation***	***Very Rare***
	Paradoxical bronchospasm	***Very Rare***
Gastro-Intestinal Disorders	***Nausea***	***Very Rare***
Musculoskeletal & Connective Tissue Disorders	***Muscle cramps***	***Common***
	Arthralgia	***Very Rare***
General Disorders and Administration Site Conditions	***Non-specific chest pain***	***Very Rare***

The pharmacological side effects of beta-2 agonist treatment, such as tremor, headache and palpitations have been reported, but tend to be transient and to reduce with regular therapy. Tremor and tachycardia occur more commonly when administered at doses higher than 50mcg twice daily.

As with other inhalational therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and fall in peak expiratory flow rate (PEFR) after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. Serevent Evohaler should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted (see Section 4.4).

4.9 Overdose

The signs and symptoms of salmeterol overdose are tremor, headache and tachycardia. The preferred antidotes are cardioselective beta-blocking agents, which should be used with caution in patients with a history of bronchospasm.

Additionally hypokalaemia can occur and therefore serum potassium levels should be monitored. Potassium replacement should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Selective beta-2-adrenoreceptor agonists.

ATC Code: R03AC12

Salmeterol is a selective long-acting (12 hour) beta-2-adrenoceptor agonist with a long side chain which binds to the exo-site of the receptor.

These pharmacological properties of salmeterol offer more effective protection against histamine-induced bronchoconstriction and produce a longer duration of bronchodilation, lasting for at least

12 hours, than recommended doses of conventional short-acting β_2 agonists. In man salmeterol inhibits the early and late phase response to inhaled allergen; the latter persisting for over 30 hours after a single dose when the bronchodilator effect is no longer evident. Single dosing with salmeterol attenuates bronchial hyper-responsiveness. These properties indicate that salmeterol has additional non-bronchodilator activity, but the full clinical significance is not yet clear. The mechanism is different from the anti-inflammatory effect of corticosteroids which should not be stopped or reduced when salmeterol is prescribed.

Salmeterol has been studied in the treatment of conditions associated with COPD and has been shown to improve symptoms, pulmonary function and quality of life.

The Salmeterol Multi-center Asthma Research Trial (SMART)

SMART was a multi-centre, randomised, double-blind, placebo-controlled, parallel group 28-week study in the US which randomised 13,176 patients to salmeterol (50μg twice daily) and 13,179 patients to placebo in addition to the patients' usual asthma therapy. Patients were enrolled if ≥12 years of age, with asthma and if currently using asthma medication (but not a LABA). Baseline ICS use at study entry was recorded, but not required in the study. The primary endpoint in SMART was the combined number of respiratory-related deaths and respiratory-related life-threatening experiences.

Key findings from SMART: primary endpoint

Patient group	Number of primary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
All patients	50/13,176	36/13,179	1.40 (0.91, 2.14)
Patients using inhaled steroids	23/6,127	19/6,138	1.21 (0.66, 2.23)
Patients not using inhaled steroids	27/7,049	17/7,041	1.60 (0.87, 2.93)
African-American patients	***20/2,366***	***5/2,319***	***4.10 (1.54, 10.90)***

(Risk in bold is statistically significant at the 95% level.)

Key findings from SMART by inhaled steroid use at baseline: secondary endpoints

	Number of secondary endpoint events /number of patients		Relative Risk (95% confidence intervals)
	salmeterol	placebo	
Respiratory -related death			
Patients using inhaled steroids	10/6127	5/6138	2.01 (0.69, 5.86)
Patients not using inhaled steroids	14/7049	6/7041	2.28 (0.88, 5.94)
Combined asthma-related death or life-threatening experience			
Patients using inhaled steroids	16/6127	13/6138	1.24 (0.60, 2.58)
Patients not using inhaled steroids	**21/7049**	**9/7041**	**2.39 (1.10, 5.22)**
Asthma-related death			

Patients using inhaled steroids	4/6127	3/6138	1.35 (0.30, 6.04)
Patients not using inhaled steroids	9/7049	0/7041	*

(*=could not be calculated because of no events in placebo group. Risk in bold is statistically significant at the 95% level. The secondary endpoints in the table above reached statistical significance in the whole population.) The secondary endpoints of combined all-cause death or life-threatening experience, all cause death, or all cause hospitalisation did not reach statistical significance in the whole population.

5.2 Pharmacokinetic properties

Salmeterol acts locally in the lung therefore plasma levels are not an indication of therapeutic effects. In addition there are only limited data available on the pharmacokinetics of salmeterol because of the technical difficulty of assaying the active substance in plasma due to the low plasma concentrations at therapeutic doses (approximately 200 picogram/ml or less) achieved after inhaled dosing.

5.3 Preclinical safety data

The only findings in animal studies with relevance for clinical use were the effects associated with exaggerated pharmacological activity.

In reproduction and development toxicity studies with salmeterol xinafoate there were no effects in rats. In rabbits, typical beta-2 agonist embryo fetal toxicity (cleft palate, premature opening of the eye lids, sternebral fusion and reduced ossification rate of the frontal cranial bones) occurred at high exposure levels (approximately 20 times the maximum recommended human daily dose based on the comparison of AUCs).

Salmeterol xinafoate was negative in a range of standard genotoxicity studies.

The non-CFC propellant, norflurane, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of up to two years including no effects on the reproductive performance or embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA 134a), a hydrofluoroalkane (non-chlorofluorocarbon) propellant

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Replace the mouthpiece cover firmly and snap it into position.

Do not store above 30° C.

Pressurised container. Do not expose to temperatures higher than 50°C. Do not puncture, break or burn even when apparently empty.

6.5 Nature and contents of container

The suspension is contained in an internally lacquered, 8ml aluminium alloy pressurised container sealed with a metering valve. The containers are fitted into plastic actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Ltd.
Stonemasons Way,
Rathfarnham, Dublin 16
Ireland

Trading as:
Allen & Hanburys
Stonemasons Way,
Rathfarnham, Dublin 16
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

MA 192/01002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

5th September 2006

10. DATE OF REVISION OF THE TEXT

7th September, 2007

SUMMARY OF PRODUCT CHARACTERISTICS

ATIMOS MODULITE 12 MICROGRAMS PRESSURISED INHALATION SOLUTION (Formoterol Fumarate Dihydrate)

Product Summary

1. NAME OF THE MEDICINAL PRODUCT

Atimos Modulite 12 micrograms/actuation pressurised inhalation solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 12 micrograms of formoterol fumarate dihydrate. This corresponds to a delivered dose of 10.1 micrograms.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Pressurised inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the long-term symptomatic treatment of persistent, moderate to severe asthma in patients requiring regular bronchodilator therapy in combination with long-term anti-inflammatory therapy (inhaled and / or oral glucocorticoids).
Glucocorticoid therapy should be continued on a regular basis.

Atimos is 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 depends on the type and severity of disease.

The following dosages are recommended for adults, including elderly patients, and adolescents aged 12 years and above:

Asthma

Adults, including the elderly, and adolescents aged 12 years and above
Usually one actuation in the morning and evening (24 micrograms of formoterol fumarate dihydrate per day). In severe cases, up to a maximum of two actuations in the morning and evening (48 micrograms of formoterol fumarate dihydrate per day).

The maximum daily dose is 4 actuations (48 micrograms of formoterol fumarate dihydrate).

Chronic Obstructive Pulmonary Disease (COPD)
Adults (aged 18 years and above)
The usual dose is one actuation twice daily (one in the morning and one in the evening, 24 micrograms formoterol fumarate dehydrate per day).
The maximum daily dose is 4 actuations (48 micrograms/day).

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 required). More than 2 inhalations should not be taken on any single occasion.

Patients should not use the inhaler beyond three months from the date of dispensing by the pharmacist (see section 6.4).

Although Atimos Modulite has a rapid onset of action, long-acting inhaled bronchodilators should be used for maintenance bronchodilator therapy.

Atimos Modulite is not intended to relieve acute asthma attacks.

In the event of an acute attack, a short-acting β_2-agonist should be used.

Patients should be advised not to stop or change their steroid therapy when Atimos Modulite is introduced.

If the symptoms persist or worsen, or if the recommended dose of Atimos Modulite fails to control symptoms (maintain effective relief), this is usually an indication of a worsening of the underlying condition.

Patients with renal or hepatic impairment

There is no theoretical reason to suggest that Atimos Modulite dosage requires adjustment in patients with renal or hepatic impairment, however, no clinical data have been generated to support its use in these groups.

Instructions for Use

To ensure proper administration of the drug, the patient should be shown how to use the inhaler by a physician or other health professional.

Before the first use of the inhaler and after 3 days or more of non-use one actuation should be discharged in the air in order to ensure a faultless function. As far as possible patients should stand or sit in an upright position when discharging the inhaler.

1. Remove the protecting cap from the mouthpiece.
2. Breathe out as deeply as possible.
3. Hold the canister vertically with its body upwards and put the mouthpiece between well-closed lips.
4. Deeply inspire through the mouth and, at the same time, press on the upper part of the inhaler to actuate the puff.
5. Hold breath as long as possible without any effort and, finally, remove the inhaler from the mouth.

Should a further puff be inhaled, the inhaler should be kept in a vertical position for about half minute, then steps 2 to 5 repeated.

After use, the mouthpiece should be closed with the protecting cap.

IMPORTANT : Steps 2 to 4 should not be performed too quickly.

Should a part of gas be sprayed from the upper part of the inhaler or from the mouth side, operations should be performed again starting from step 2.

For patients with weak hand-grip it could be easier to hold the inhaler with both hands. Therefore, the upper part of the inhaler is held with both index fingers and its lower part is held with both thumbs.

The use of a spacer device with the inhaler is usually recommended for patients who have difficulty in coordinating inhalation with actuation, however, no clinical data are available for Atimos Modulite with spacers.

4.3 Contraindications

Contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Atimos Modulite should be used strictly in accordance with the dosage recommendations (see section 4.2).

If there is no satisfactory improvement or even a deterioration of the disease despite the prescribed therapy, a consultation with a physician will be necessary to modify the therapeutic program, if appropriate, by adding additional medicinal products.

A sudden and progressive deterioration of the asthmatic disorder can be life-threatening and requires immediate medical intervention.

Considerably exceeding the prescribed individual doses or the total daily dose can be hazardous due to the effects on the heart (cardiac arrhythmia, rise in blood pressure), in combination with changes in the salt concentrations in body fluids (electrolyte shifts), and must therefore be avoided.

Until extensive experience is available, Atimos Modulite should not be used in children.

Concomitant conditions
Atimos Modulite should only be used with caution and under strict conditions of indication in patients with third degree atrioventricular block, idiopathic subvalvular aortic stenosis, hypertrophic obstructive cardiomyopathy, QT-interval prolongation, eg. congenital or drug-induced (QTc > 0.44 seconds), thyrotoxicosis, severe heart disease, especially acute myocardial infarction, coronary heart disease, congestive heart failure, occlusive vascular diseases, especially arteriosclerosis, arterial hypertension and aneurysm, hyperthyreosis, refractory diabetes mellitus, phaeochromocytoma.

Atimos Modulite may only be used with special precautions (eg. monitoring) in patients with tachycardic arrhythmia (accelerated and / or irregular heart beat). The inhalation of high doses of formoterol may cause a rise in blood sugar levels. This parameter should therefore be closely monitored in diabetics. If anaesthesia with halogenated anaesthetics is planned, it should be ensured that Atimos Modulite is not administered for at least 12 hours before the start of anaesthesia.

Paradoxical bronchospasm
As with every inhalation therapy, paradoxical bronchospasm can occur in rare cases. In such cases the medicinal product should be discontinued immediately and the therapeutic program should be modified by the physician.

Hypokalaemia
There is evidence that under formoterol therapy the decrease of blood potassium levels is higher than during treatment with short acting β_2-sympathomimetics (eg. Salbutamol). Therefore potassium levels have to be regularly monitored particularly in patients with low basic potassium values or peculiar risks for decreased blood potassium levels. The monitoring should also be conducted if no decreased levels occurred under previous treatment with short acting β_2-sympathomimetics. Where applicable, potassium has to be substituted.

The hypokalaemia may be particularly distinctive in patients with severe asthma receiving concomitant treatment with theophylline, glucocorticoids and/or diuretics. Due to decreased serum potassium levels the effect of digitalis containing medicinal products is enhanced.

As the risk related to hypokalaemia is potentiated by hypoxia care should be taken in patients with acute severe asthma.

4.5 Interactions with other medicinal products and other forms of interaction

Drugs such as quinidine, disopyramide, procainamide, phenothiazines, antihistamines and tricyclic antidepressants may be associated both with QT-interval prolongations and an increased risk of ventricular arrhythmia (see section 4.3).

Concomitant administration of other sympathomimetic agents may potentiate the undesirable effects of Atimos Modulite.

The simultaneous use of formoterol and theophylline can result in mutual potentiation of effects, and there is also the likelihood of increased undesirable effects such as cardiac dysrhythmia. Compounds which themselves potentiate sympathomimetic effects, such as L-dopa, L-thyroxine, oxytocin or alcohol, can also affect cardiovascular regulation when taken at the same time as formoterol.

Administration of Atimos Modulite to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants should be performed with caution, since the action of β_2-adrenergic stimulants on the cardiovascular system may be potentiated.

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate a possible hypokalaemic effect of β_2-agonists. Hypokalaemia may increase susceptibility to cardiac arrhythmias in patients treated with digitalis (see section 4.4).

β-adrenergic blockers may weaken or antagonise the effect of Atimos Modulite. Therefore, Atimos Modulite should not be given together with β-adrenergic blockers (including eye drops) unless there are compelling reasons for their use.

4.6 Pregnancy and lactation

Insufficient experience is presently available with the use of formoterol during human pregnancy. Although no embryotoxic or teratogenic effects were detected in animal studies, the use of formoterol during pregnancy, especially during the first 3 months, is only indicated if absolutely necessary.

The known tocolytic action of β_2-sympathomimetic agents of the type contained in Atimos Modulite requires a close benefit-risk assessment before using this medicinal product shortly before delivery.

While it is not known whether formoterol passes into human breast milk, it has been detected in the milk of lactating animals. Mothers using formoterol should therefore refrain from breast feeding their infants.

4.7 Effects on ability to drive and use machines

Atimos Modulite is unlikely to have any effect on the ability to drive and operate machinery.

4.8 Undesirable effects

The frequency of Adverse Reactions has been classified as follows :
Common (> 1/100 < 1/10)

Uncommon (> 1/1,000 < 1/100)
Rare (> 1/10,000 < 1/1,000)
Very rare (< 1/10,000) including isolated reports

Blood and lymphatic system disorders
Very rare including isolated reports : thrombopenia

Cardiac disorders
Common : palpitations
Uncommon : tachycardia, tachyarrhythmia
Rare : ventricular extrasystoles, angina pectoris
Very rare including isolated reports : atrial fibrillation

Gastrointestinal disorders
Uncommon : nausea, dysgeusia

General disorders and admnistration site conditions
Very rare including isolated reports : peripheral oedema

Immune system disorders
Rare : angioneurotic oedema

Investigations
Uncommon : blood insulin increased, free fatty acids increased, blood ketone body increased
Rare : blood pressure increased, blood pressure decreased

Metabolism and nutrition disorders
Uncommon : hypokalaemia, hyperglycaemia

Musculoskeletal and connettive tissue disorders
Uncommon : muscle cramps, myalgia

Nervous system disorders
Common : tremor, headache
Uncommon : restlessness, dizziness
Very rare including isolated reports : CNS stimulating effects have been sporadically reported following inhalation of β_2-sympathomimetics, manifesting as hyperexcitability. These effects were mainly observed in children up to 12 years of age.

Psychiatric disorders
Very rare including isolated reports : abnormal behaviour, sleep disorders, hallucinations

Renal and urinary disorders
Rare : nephritis

Respiratory, thoracic and mediastinal disorders
Common : cough
Uncommon : throat irritation
Rare : paradoxical bronchospasm
Very rare including isolated reports : dyspnoea, exacerbation of asthma

Skin and subcutaneous tissue disorders
Uncommon : pruritus, exanthem, hyperhidrosis
Rare : urticaria

Tremor, nausea, dysgeusia, throat irritation, hyperhidrosis, restlessness, headache, dizziness and muscle cramps may resolve spontaneously within one to two weeks of continued treatment.

4.9 Overdose

There is no clinical experience to date on the management of overdose, however, an overdosage of Atimos Modulite would be likely to lead to effects that are typical of β_2-adrenergic agonists : nausea, vomiting, headache, tremor, somnolence, palpitations, tachycardia, ventricular arrhythmias, metabolic acidosis, hypokalaemia, hyperglycaemia.

Treatment of Overdose
Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective β-adrenergic 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

Pharmacodynamic properties

Pharmacotherapeutic Group: Adrenergics, inhalants; selective β_2-adrenoreceptor agonists
ATC code : R03A C13

Formoterol is a predominantly selective β_2-stimulator. Formoterol has bronchodilator activity in patients with reversible obstructive airway diseases. The onset of action is observed within one to three minutes. Significant bronchodilation is still present 12 hours after inhalation.

In humans formoterol is effective in the prophylaxis of bronchospasm induced by methacoline challenge.

5.2 Pharmacokinetic properties

Absorption
As with other substances administered by inhalation, 90 % of the inhaled formoterol dose is swallowed and absorbed from the gastrointestinal tract. The pharmacokinetic characteristics of the oral formulation can thus be extrapolated to the inhalation of metered aerosol.

Absorption is both rapid and extensive; after inhalation of a therapeutic dose (12 micrograms) of Atimos Modulite pressurised inhalation solution in asthmatic patients, the peak plasma concentration is observed approximately 15 minutes after inhalation, earlier than that observed with a formoterol powder inhalation. Generally, absorption rate should be taken into account when switching patients from one formoterol formulation to another.

Absorption of formoterol is linear following inhalation of 12 micrograms to 96 micrograms of formoterol fumarate dihydrate.

Oral doses of up to 300 micrograms of formoterol are rapidly absorbed from the gastrointestinal tract. The peak plasma concentration of the unchanged substance is reached after 30 minutes to 1 hour. More than 65 % of an oral dose of 80 micrograms is absorbed.

Dose linearity is present within a dose range of 20 micrograms to 300 micrograms (oral administration).

Repeated daily administration of 40 micrograms to 160 micrograms per day does not result in accumulation because of the short half-life. The pharmacokinetics of formoterol does not differ significantly between men and women.

Distribution
Plasma protein binding is 61 % to 64 % (34 % to albumin); binding sites are not saturated at therapeutic dose levels.

Metabolism
Formoterol is metabolised primarily via direct glucuronisation and is eliminated completely. A further route of biotransformation is O-demethylation followed by glucuronisation with consecutive complete elimination.

Multiple CYP450 isozymes catalyze the transformation (2D6, 2C19, 2C9, and 2A6) and consequently the potential for metabolic drug-drug interaction is low. The kinetics of formoterol are similar after single and repeated administration, indicating no auto-induction or inhibition of metabolism**.**

Elimination
The elimination of formoterol apparently follows a polyphasic pattern, and the half-life described is therefore dependent on the time intervals considered. Based on plasma or blood concentrations measured 6, 8 or 12 hours after oral administration, an elimination half-life of 2 to 3 hours was determined. A half-life of 5 hours was calculated from the renal excretion rate between 3 and 16 hours after inhalation.

The active substance and metabolites are eliminated completely, two thirds of an oral administered dose with the urine, one third with the faeces. Following inhalation of formoterol, a mean of 6 % to 9 % of the substance is eliminated unchanged with the urine. Renal clearance of formoterol is 150 ml per minute.

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 very high systemic exposure of 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 in rodents after long exposure to high doses of β_2-agonists.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Norflurane (HFA-134a)
Ethanol anhydrous
Hydrochloric acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months (see also section 6.4)

6.4 Special precautions for storage

Prior to dispensing to the patient
Store in a refrigerator at 2 °C to 8 °C (for a maximum of 15 months)

After dispensing
Do not store above 30 °C (for a maximum of 3 months)

6.5 Type and contents of container

A pressurised, aluminium canister fitted with a metering valve, actuator and dust cap.

Each canister provides 50, 100 or 120 actuations.

6.6 Special precautions for disposal

For pharmacies
Enter the date of dispensing to the patient on the pack.

Ensure that there is a period of at least 3 months between the date of dispensing and the expiry date printed on the pack.

ADMINISTATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Trinity-Chiesi Pharmaceuticals Limited
Cheadle Royal Business Park
Highfield
Cheadle
SK8 3GY
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 08829/0154

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

29/09/2005

10. DATE OF REVISION OF THE TEXT

06/2007

11. LEGAL CATEGORY

POM