OXIS® TURBUHALER®

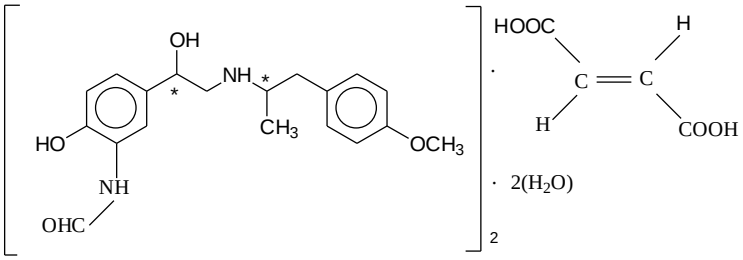
PRODUCT INFORMATION

NAME OF THE MEDICINE

Eformoterol fumarate dihydrate is now known as formoterol fumarate dihydrate. For convenience the term formoterol has been used throughout this document.

The chemical name is (R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate.

The chemical structure of formoterol fumarate dihydrate is:



CAS number: CAS 43229-80-7

DESCRIPTION

Oxis Turbuhaler contains formoterol fumarate dihydrate. Two strengths are available (refer *Presentations and storage conditions* for details). Formoterol is a potent selective β_2-adrenergic stimulant that produces relaxation of bronchial smooth muscle. In addition to the active substance formoterol fumarate dihydrate, Oxis Turbuhaler also contains the inactive ingredient lactose monohydrate. The product is free from other additives such as propellants, lubricants, preservatives or carrier substances.

PHARMACOLOGY

Formoterol is a potent selective β_2-adrenergic stimulant that produces relaxation of bronchial smooth muscle. Therefore it has a bronchodilating effect in patients with reversible airways obstruction and in patients with bronchospasm induced by direct (methacholine) and indirect (eg exercise) stimuli. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation and has a mean duration of 12 hours following a single dose.

Pharmacokinetics

Absorption

Inhaled formoterol is rapidly absorbed and peak plasma concentrations are reached about 15 minutes after inhalation. In clinical studies, the mean lung deposition of formoterol after inhalation via Turbuhaler (M2 version) 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).

In a pharmacokinetic study with the M3 Turbuhaler version, the mean lung deposition of formoterol after inhalation via Turbuhaler was 43% of the delivered dose (corresponding to 32% of the metered dose).

Distribution and metabolism

Plasma protein binding is approximately 50%. Formoterol is metabolised via direct glucuronidation and O-demethylation.

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 the M2 version) of formoterol is excreted unmetabolised in the urine. The terminal half-life after inhalation is estimated to 8 hours.

CLINICAL TRIALS

Oxis Turbuhaler

The clinical data provided below refers to the metered dose (amount of formoterol from the metering unit) of the Oxis Turbuhaler M2 version. The corresponding delivered doses (amount of formoterol from the Turbuhaler mouthpiece) are discussed within the *Presentations and storage conditions* section below.

The M3 version of Oxis Turbuhaler (refer *Presentations and storage conditions* section) has been shown to be therapeutically equivalent to the original Oxis Turbuhaler M2 version.

Asthma – continuous prophylactic use

The clinical efficacy studies conducted with Oxis Turbuhaler (M2 version) include 7 blinded controlled trials (parallel group and crossover). A total of 1353 adult patients with bronchial asthma were randomised and treated with treatment periods ranging from 2 to 24 weeks. Two open, uncontrolled, long-term trials were also performed in 201 patients who had participated in short-term treatment.

The primary objective of the controlled clinical studies was to evaluate the efficacy of Oxis Turbuhaler in comparison with placebo and/or an active control (terbutaline, formoterol pMDI and budesonide).

Efficacy has also been studied in three single-dose, placebo-controlled, cross over studies performed in a total of 87 patients with asthma, to determine the dose-response relationship for doses of 3 µg up to 48 µg of Oxis Turbuhaler.

Asthma – as needed use

Two large double-blind, randomised, parallel studies have been conducted in moderate to severe asthmatic patients on continual prophylactic corticosteroid therapy with Oxis Turbuhaler (M2 version; 72 µg metered dose maximal daily dose) as prn (as needed use) treatment for 12 weeks.

One study compared prn Oxis Turbuhaler to prn terbutaline Turbuhaler (6 mg maximal daily dose) in 362 adult patients on prophylactic inhaled corticosteroid therapy. The other study compared prn Oxis Turbuhaler to prn terbutaline Turbuhaler (6 mg maximal daily dose) in 357 adult patients on prophylactic inhaled Oxis Turbuhaler (12 µg metered dose bid) and inhaled corticosteroids. The two trials showed that Oxis Turbuhaler could replace terbutaline Turbuhaler for rescue treatment without loss of efficacy. There were no differences of clinical significance with respect to prn inhalations per day, peak expiratory flow rate, incidence of exacerbations or asthma score.

INDICATIONS

Long-term treatment of reversible airways obstruction in asthma (including nocturnal asthma and exercise induced asthma) in adults and children aged 12 years and over who are receiving inhaled or oral corticosteroids and who require bronchodilator therapy.

Oxis Turbuhaler can be used on demand (prn) in asthmatics over the age of 18 years who are receiving inhaled or oral corticosteroids. It should not be used in patients whose asthma can be managed alone by occasional use of short acting inhaled β_2-agonists.

CONTRAINDICATIONS

Hypersensitivity to formoterol or lactose.

PRECAUTIONS

Formoterol should not be initiated in patients to treat an acute severe asthma exacerbation, or if they have significantly worsening or acutely deteriorating asthma.

Asthma action plan

Patients with asthma should have a personal asthma action plan designed in association with their general practitioner. This plan should incorporate a stepwise treatment regimen which can be instituted if the patient's asthma deteriorates. It should include advice as to when urgent medical attention is required and that patients should not stop other asthma treatments, even if they feel better, without seeking medical advice.

Anti-inflammatory therapy

Formoterol is not a substitute for anti-inflammatory therapy with inhaled or oral corticosteroids. Asthmatic patients who require regular therapy with β_2-adrenoceptor agonists should also receive regular and adequate doses of inhaled or oral corticosteroids. Whenever formoterol is prescribed, patients should be evaluated for the adequacy of their corticosteroid treatment. Patients must be advised to continue taking their corticosteroid therapy unchanged after the introduction of formoterol even when their symptoms improve.

Lack of response

If a previously effective dosage regimen of bronchodilators no longer gives the same symptomatic relief the patient should seek medical advice as soon as possible since this could be an indication of worsening asthma.

Sensitivity to sympathomimetic amines

In patients with increased susceptibility to sympathomimetic amines (eg inadequately controlled hyperthyroidism), formoterol should be used with caution.

Diabetes

Due to the blood-glucose increasing effects of β_2-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on formoterol

Arrhythmogenic potential

β_2-agonists have an arrhythmogenic potential which must be considered before commencing treatment for bronchospasm.

Other cardiovascular conditions

The effects of formoterol in acute as well as chronic toxicity studies were seen mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These are known pharmacological manifestations seen after administration of high doses of β-adrenoceptor agonists.

Patients with pre-existing cardiovascular conditions are at greater risk of developing adverse cardiovascular effects following administration of formoterol. Caution is advised when formoterol is administered to patients with severe cardiovascular disorder, such as ischaemic heart disease, tachyarrythmias or severe heart failure.

Hypokalaemia

Potentially serious hypokalaemia may result from β_2-stimulant therapy. Particular caution is advised in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments (see *Interactions with other medicines* section). Patients receiving digoxin are particularly sensitive to hypokalaemia. Serum potassium levels should therefore be observed in such situations.

Impaired renal and hepatic function

The effect of decreased liver and kidney function on the pharmacokinetics of formoterol is not known. As formoterol is primarily eliminated via hepatic metabolism, increased plasma levels of formoterol would be expected in patients with severe liver cirrhosis.

Lactose

Oxis Turbuhaler contains lactose monohydrate (<0.9 mg/inhalation delivered dose) which may contain milk protein residue. This amount does not normally cause problems in lactose intolerant people.

Effects on fertility

Long term treatment of female mice and rats with formoterol fumarate causes ovarian stimulation, the development of ovarian cysts and hyperplasia of granulosa/theca cells as a result of the β-agonist properties of the compound. A study by another company showed no effect on fertility of female rats dosed orally with formoterol fumarate at 60 mg/kg/day for two weeks. This finding was repeated in an Astra study where no effect was seen on the fertility of female rats dosed orally with formoterol fumarate at 15 mg/kg/day for 2 weeks.

Testicular atrophy was observed in mice given formoterol fumarate in the diet at 0.2-50 mg/kg/day for two years, but no effect on male fertility was observed in rats dosed orally at 60 mg/kg/day for nine weeks, in studies undertaken by another company.

Use in pregnancy (Category B3)

No teratogenic effects were observed in rats receiving formoterol fumarate at doses up to 60 mg/kg/day orally or 1.2 mg/kg/day by inhalation. Fetal cardiovascular malformations were observed in one study in which pregnant rabbits were dosed orally at 125 or 500 mg/kg/day during the period of organogenesis, but similar results were not obtained in another study at the same dose range. In a third study, an increased incidence of subcapsular hepatic cysts was observed in fetuses from rabbits dosed orally at 60 mg/kg/day. Decreased birth weight and increased peri/postnatal mortality were observed when formoterol fumarate was given to rats at oral doses of 0.2 mg/kg/day or greater during late gestation.

Clinical experience with Oxis Turbuhaler in pregnant women is limited. Effects seen in animal studies were at considerably higher systemic exposures than those in clinical use. Since asthma control is important for maternal and fetal health, use of Oxis Turbuhaler in pregnancy should be considered when indicated.

β_2-adrenoceptor agonists including formoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Use in lactation

Formoterol has been detected in small amounts in the milk of lactating rats, but it is not known whether formoterol passes into human breast milk.

A study in rats showed increased postnatal mortality at maternal oral doses of 0.2 mg/kg/day or greater, and retardation of pup growth at 15 mg/kg/day.

Since asthma control is important for maternal and foetal health, use of Oxis Turbuhaler in women who are breastfeeding should be considered when indicated.

Use in children

Oxis is not recommended for children under 12 years old.

Genotoxicity

Mutagenicity tests covering a range of experimental endpoints have been conducted. No genotoxic effects were found in any of the *in vitro* or *in vivo* tests, except for a slight increase in reverse mutation frequency in *Salmonella typhimurium* at high concentrations of formoterol fumarate.

Carcinogenicity

In carcinogenicity studies performed by Astra, there was a dose-dependent increase in the incidence of uterine leiomyomas in mice dosed orally at 0.1, 0.5 and 2.5 mg/kg/day for two years, and a mesovarian leiomyoma was observed in a female rat dosed by inhalation at 0.13 mg/kg/day for two years. The effects observed are expected findings with high dose exposure to β_2-agonists.

In carcinogenicity studies performed by other companies, very high dose levels were used, resulting in systemic exposure levels 800-4800 fold higher than those expected upon clinical use of formoterol (based on an 18 µg daily dose). The studies are summarised below.

In the initial studies performed by other companies, addition of formoterol fumarate to the drinking water caused adrenal subcapsular cell tumours in male mice dosed at 66-225 mg/kg/day, thyroid C-cell neoplasms in male rats dosed at 46 mg/kg/day, mesovarian leiomyomas in female rats dosed at 18-72 mg/kg/day, and an increased incidence of mammary adenocarcinoma in female rats dosed at 36-72 mg/kg/day.

In the repeated studies performed by other companies, drug was administered with the feed. Hepatocellular adenomas and carcinomas were observed in male and female mice at dose levels greater than 2 mg/kg/day, and leiomyomas and leiomyosarcomas were seen in the reproductive tract of female mice dosed at 2-50 mg/kg/day. Mesovarian leiomyomas were observed in rats dosed at 2-20 mg/kg/day, and benign granulosa/theca cell tumours in the ovaries of rat dosed at 0.5-20 mg/kg/day. Plasma drug concentrations at dose levels associated with these carcinogenic effects, based on AUC values, were estimated to be at

least ten times higher than the maximum systemic exposure anticipated in humans.

Mammary adenocarcinomas, smooth muscle tumours in the female reproductive system and effects on the ovary have been reported in rats or mice treated with other β_2-adrenoceptor agonists, and are likely to be secondary to prolonged stimulation of β_2-adrenoceptors in these tissues.

Thyroid C-cell tumours were only seen at doses resulting in systemic exposure several fold higher than that expected at the highest recommended human dose. They are thought to be a consequence of stimulation of calcitonin secretion as a result of bone growth, secondary to β-agonist induced anabolic effects on skeletal muscle at excessive formoterol doses. The mechanism underlying the induction of hepatocellular tumours and adrenal subcapsular tumours in the mouse is unclear.

However, in view of the dose levels at which these effects were observed and the fact that formoterol is not mutagenic (except for very weak activity at high concentrations in one test system), it is concluded that the cancer risk in patients treated with formoterol fumarate is no greater than for other β-adrenoceptor agonists.

Effect on driving or operating machinery

Oxis Turbuhaler does not affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

β-receptor blocking agents

β-receptor blocking agents, especially those which are non-selective, may partly or totally inhibit the effect of β-agonists. These medicines may also increase airway resistance, therefore the use of these medicines in asthma patients is not recommended.

Other sympathomimetic agents

Other β-adrenergic stimulants or sympathomimetic amines such as ephedrine should not be given concomitantly with formoterol since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given formoterol

Xanthine derivatives, mineralocorticosteroids and diuretics

Hypokalaemia may result from β_2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, mineralocorticosteroids, and diuretics, such as thiazide and loop diuretics (see *Precautions – Other cardiovascular conditions* section).

Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines, antihistamines and erythromycin

The adverse cardiovascular effects of formoterol may be exacerbated by concurrent administration of medicines associated with QT interval prolongation and increased risk of ventricular arrhythmia. For this reason caution is advised when formoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines, erythromycin or antihistamines (eg astemizole, terfenadine, mizoblastine).

ADVERSE EFFECTS

Pharmacologically predictable side-effects of β_2-agonist therapy, such as tremor and palpitations, may occur, but tend to be transient and are reduced with regular therapy.

Frequency	System Organ Class	Event
Common (≥1% - <10%)	Nervous system disorders	Headache*, tremor, dizziness
	Gastrointestinal disorders	Nausea
	Musculoskeletal & connective tissue disorders	Muscle cramps
Uncommon (≥0.1% - <1%)	Cardiac disorders	Palpitations; Tachycardia; cardiac arrhythmias eg atrial fibrillation, supraventricular tachycardia & extrasystoles; angina pectoris
	Psychiatric disorders	Sleep disturbances
	Immune system disorders	Hypersensitivity reactions eg bronchospasm, exanthema, urticaria, pruritus
	Metabolism & nutrition disorders	Hypokalaemia; hyperglycaemia
	Nervous system disorders	Taste disturbance
	Vascular disorders	Variations in blood pressure
Rare (≥0.01 - <0.1%)	Psychiatric disorders	Agitation, restlessness

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

As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. Treatment with β-sympathomimetics may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

DOSAGE AND ADMINISTRATION

The doses below are provided as the metered dose of the Oxis Turbuhaler M2 version with the corresponding delivered dose in brackets afterwards. Refer *Presentations and storage conditions* for further details.

The dosage of formoterol via Oxis Turbuhaler should be individualised. The treatment should always aim for the lowest effective dose.

The recommended dose is 6-12 µg (corresponding to 4.5-9 µg delivered dose) twice daily, however some patients may require a dose of up to 24 µg (corresponding to 18 µg delivered dose) twice daily. During regular twice daily dosing, a total daily dose of 48 µg (corresponding to 36 µg delivered dose) in adults and 24 µg (corresponding to 18 µg delivered dose) in children 12 years and over should not be exceeded.

In patients over the age of 18 years on regular corticosteroids and regular formoterol, additional doses of formoterol can be administered as required for the relief of symptoms. The maximum total daily dose should not normally exceed 72 µg (corresponding to 54 µg delivered dose). Prolonged use (more than 3 consecutive days) of more than 48 µg (corresponding to 36 µg delivered dose) is a sign of sub-optimal asthma control and treatment should be reassessed.

There is no evidence of efficacy of formoterol in acute severe asthma exacerbations.

Impaired renal and hepatic function

No adjustment of dose should be required in patients with renal or hepatic impairment at the recommended doses. However, no clinical studies have been performed in these groups.

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 that are provided with each pack of Oxis Turbuhaler
- Breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- Never breathe out through the mouthpiece
- Replace the cover of Oxis Turbuhaler after use

The patient may not taste or feel any medication when using Turbuhaler due to the small amount of medicine delivered.

OVERDOSAGE

Possible symptoms and signs

An overdose would be likely to lead to effects typical of β_2-adrenergic agonists such as tremor, headache, palpitations, and tachycardia. Hypotension, metabolic acidosis, hypokalaemia, hyperglycaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting may also occur. The symptoms and signs are those characteristic of excessive sympathetic stimulation.

Laboratory findings

Monitoring of serum potassium concentrations may be warranted. β_2-agonists may cause hypokalaemia as a result of redistribution of potassium, but this usually requires no treatment.

Treatment

There is no clinical experience on the management of overdose with formoterol, however supportive and symptomatic treatment may be indicated. β-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Oxis is available in a multi-dose, inspiratory flow driven, metered dose dry powder inhaler (Turbuhaler). Oxis Turbuhaler contains 60 doses and is available in two strengths. The Oxis M2 Turbuhaler version was labelled as the metered dose (amount of formoterol from the metering unit) – 6 and 12 µg/inhalation. The M2 and M3 Turbuhaler versions of Oxis both deliver (amount of formoterol leaving the mouthpiece) the same dose to the patient (4.5 and 9 µg/inhalation respectively), however the metered dose cannot be measured in the M3 Turbuhaler version. To avoid confusion the new M3 Turbuhaler version of Oxis is labelled with the corresponding metered dose of the M2 Turbuhaler version in addition to the delivered dose. The following table provides the corresponding dose delivered to the patient.

Oxis	**Metered dose (µg/inhalation)**		**Delivered dose (µg/inhalation)**
	M2 version	**M3 version**	**M2 and M3 version**
6	6	Not able to be measured	4.5*
12	12	Not able to be measured	9*

* Doses referred to in majority of Oxis publications

Storage conditions

Oxis Turbuhaler should be stored with the cover firmly in place at a temperature below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

10th November 1997 (M2 version)

DATE OF MOST RECENT AMENDMENT

8th May 2017