NAME OF THE DRUG

Eformoterol fumarate dihydrate. The chemical name is (R*R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butenedioate(2:1), dihydrate. CAS 43229-80-7. The chemical structure of eformoterol fumarate dihydrate is:

\[
\text{HO} \quad \text{OH} \quad \text{NH} \quad \text{CH}_3 \quad \text{OCH}_3 \\
\text{NH} \quad \text{OHC} \\
\text{HOOC} \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{COOH} \\
\text{2(H}_2\text{O)}
\]

DESCRIPTION

OXIS TURBUHALER contains eformoterol fumarate dihydrate, 6 μg or 12 μg per metered dose. Eformoterol is a potent selective β₂-adrenergic stimulant that produces relaxation of bronchial smooth muscle. In addition to the active substance eformoterol fumarate dihydrate, OXIS TURBUHALER contains lactose as the only constituent. The product is free from other additives such as propellants, lubricants, preservatives or carrier substances.

PHARMACOLOGY

Eformoterol is a potent selective β₂-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 (e.g. 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

Inhaled eformoterol is rapidly absorbed and peak plasma concentrations are reached about 15 minutes after inhalation. In clinical studies, the mean lung deposition of eformoterol after inhalation via Turbuhaler ranged from 21-37% of the metered dose. The total systemic availability for the higher lung deposition was around 46%.
Following inhalation, the major part of the dose of eformoterol is metabolised via direct glucuronidation and $\text{O}$-demethylation, then eliminated. Only 6-10% of the metered dose is excreted unmetabolised in the urine. The terminal half-life of eformoterol after inhalation is estimated at 8 hours.

In humans, approximately 50% of eformoterol is bound to plasma proteins.

**Clinical Trials**

In studies with OXIS TURBUHALER 149 healthy subjects and 2514 patients in total have been randomised.

**Asthma – continuous prophylactic use**

The clinical efficacy studies conducted with OXIS TURBUHALER 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, eformoterol 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 (72 µg metered dose maximal daily dose) as p.r.n. (as needed use) treatment for 12 weeks.

One study compared p.r.n. OXIS TURBUHALER to p.r.n. terbutaline Turbuhaler (6 mg maximal daily dose) in 362 adult patients on prophylactic inhaled corticosteroid therapy. The other study compared p.r.n. OXIS TURBUHALER to p.r.n. terbutaline Turbuhaler (6 mg maximal daily dose) in 357 adult patients on prophylactic inhaled OXIS TURBUHALER (12 µg metered dose b.i.d) 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 p.r.n. 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 (p.r.n.) 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 β2-agonists.

**CONTRAINDICATIONS**

Hypersensitivity to eformoterol or lactose.

**PRECAUTIONS**

Eformoterol 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_
Eformoterol is not a substitute for anti-inflammatory therapy with inhaled or oral corticosteroids. Asthmatic patients who require regular therapy with β2-adrenoceptor agonists should also receive regular and adequate doses of an inhaled or oral corticosteroids. Whenever eformoterol 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 eformoterol, 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 (e.g. inadequately controlled hyperthyroidism), eformoterol should be used with caution.

_Diabetes_
Due to the blood-glucose increasing effects of β2-stimulants extra blood glucose controls are initially recommended when diabetic patients are commenced on eformoterol.

_Arrhythmogenic potential_
β2-agonists have an arrhythmogenic potential which must be considered before commencing treatment for bronchospasm.
Other cardiovascular conditions
The effects of eformoterol 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 eformoterol. Caution is advised when eformoterol is administered to patients with severe cardiovascular disorder, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

Hypokalaemia
Potentially serious hypokalaemia may result from β₂-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 Drugs” section). Patient 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 eformoterol is not known. As eformoterol is primarily eliminated via hepatic metabolism, increased plasma levels of eformoterol would be expected in patients with severe liver cirrhosis.

Other
OXIS TURBUHALER contains lactose (< 0.6 mg/inhalation) which may contain milk protein residue. This amount does not normally cause problems in lactose intolerant people.

Carcinogenicity / Mutagenicity / Impairment of Fertility

Mutagenicity
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 eformoterol 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 β₂-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 eformoterol (based on an 18 μg daily dose). The studies are summarised below.
In the initial studies performed by other companies, addition of eformoterol 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 β2-adrenoceptor agonists, and are likely to be secondary to prolonged stimulation of β2-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 eformoterol 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 eformoterol 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 eformoterol fumarate is no greater than for other β-adrenoceptor agonists.

**Impairment of fertility**

Long term treatment of female mice and rats with eformoterol 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 eformoterol 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 eformoterol fumarate at 15 mg/kg/day for 2 weeks.

Testicular atrophy was observed in mice given eformoterol 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 eformoterol 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 doses orally at 60 mg/kg/day. Decreased birth weight and increased peri/postnatal mortality were observed when eformoterol 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 foetal health, use of OXIS TURBUHALER in pregnancy should be considered when indicated.

β2-adrenoceptor agonists including eformoterol may inhibit labour due to a relaxant effect on uterine smooth muscle.

Use in Lactation
Eformoterol has been detected in small amounts in the milk of lactating rats, but it is not known whether eformoterol 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.

Effect on driving or operating machinery
OXIS TURBUHALER does not affect the ability to drive or use machines.

Interactions With Other Drugs
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 drugs may also increase airway resistance, therefore the use of these drugs 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 eformoterol, since the effects will be cumulative. Patients who have already received large doses of sympathomimetic amines should not be given eformoterol.
**Xanthine derivatives, mineralocorticosteroids and diuretics**

Hypokalaemia may result from β₂-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 eformoterol may be exacerbated by concurrent administration of drugs associated with QT interval prolongation and increased risk of ventricular arrhythmia. For this reason caution is advised when eformoterol is administered to patients already taking monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines, erythromycin or antihistamines (eg, astemizole, terfenadine, mizoblastine).

**ADVERSE REACTIONS**

Pharmacologically predictable side-effects of β₂-agonist therapy, such as tremor and palpitations, may occur, but tend to be transient and are reduced with regular therapy. As for all β₂-agonists, cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles have been rarely reported. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases.

*The following definitions of frequency are used:*

very common ≥ 10%; common 1 - 9.9%; uncommon 0.1 - 0.9%; rare 0.01 - 0.09%; very rare < 0.01%.

**Musculoskeletal system**

*Common:* tremor

*Uncommon:* muscle cramps

**Cardiovascular system**

*Common:* palpitations

*Uncommon:* tachycardia

**Central nervous system**

*Common:* headache

*Uncommon:* agitation, restlessness, sleep disturbances

**Respiratory tract**

*Rare:* bronchospasm

**Skin**

*Rare:* exanthema, urticaria, pruritus

**Metabolic**

*Rare:* hypokalaemia

**Gastrointestinal disorders**

*Rare:* Nausea
In isolated cases the following undesirable effects have been reported: taste disturbance, dizziness, angina pectoris, variations in blood pressure and hyperglycaemia.

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 dosage of eformoterol via OXIS TURBUHALER should be individualised. The treatment should always aim for the lowest effective dose.

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

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

There is no evidence of efficacy of eformoterol 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.

Patients should be advised that OXIS TURBUHALER should be discarded after 60 doses have been taken. This is indicated by a red mark appearing in a window on the device.

**OVERDOSAGE**

**Possible symptoms and signs**

An overdose would be likely to lead to effects typical of β2-adrrenergic 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. β2-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 eformoterol, 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.

**PRESENTATION**
OXIS TURBUHALER contains 6 and 12 micrograms per inhalation in a multidose, inspiratory flow driven, metered dose powder inhaler. The device contains 60 doses and is made of plastic parts.

**STORAGE**
OXIS TURBUHALER should be stored with the cover firmly in place at a temperature below 30°C.

**NAME AND ADDRESS OF DISTRIBUTOR**
AstraZeneca Pty Ltd
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