

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

OXIS® 6 TURBUHALER®, 4.5 micrograms/inhalation, Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose contains 4.5 micrograms eformoterol fumarate dihydrate. The corresponding metered dose contains 6 micrograms eformoterol fumarate dihydrate.

Excipients with known effect

Lactose monohydrate 895.5 micrograms per delivered dose. See section 4.4 Special Warnings and Precautions for Use.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Asthma

OXIS 6 TURBUHALER is indicated as add on therapy to maintenance treatment with inhaled corticosteroids for the treatment of broncho-obstructive symptoms and prevention of exercise-induced symptoms in adults and children six years of age and over with asthma when adequate treatment with corticosteroids is not sufficient.

OXIS 6 TURBUHALER should not be used in the treatment of acute asthmatic symptoms or in patients whose asthma can be managed by occasional use of short-acting beta-2 agonists.

Chronic Obstructive Pulmonary Disease (COPD)

OXIS 6 TURBUHALER is indicated for the relief and prevention of broncho-obstructive symptoms in adults with chronic obstructive pulmonary disease (COPD).

4.2 DOSAGE AND METHOD OF ADMINISTRATION

ASTHMA

OXIS 6 TURBUHALER must not be administered as monotherapy in the management of asthma. In these patients, OXIS 6 TURBUHALER (as with other long-acting beta-2 agonists) must only be used in combination with anti-inflammatory therapy such as inhaled corticosteroids.

The dosage of OXIS 6 TURBUHALER should be individualised for each patient and should be used at the lowest effective dose required to achieve control of asthma symptoms.

Patients should be advised not to take additional doses to treat acute asthmatic symptoms, but to take a short-acting inhaled beta-2 agonist.

Adults

Regular Maintenance Dosing

One to two inhalations (6 to 12 µg eformoterol, corresponding to 4.5 – 9 µg delivered dose) once or twice daily. Some patients may need up to four inhalations (24 µg, corresponding to 18 µg delivered dose) once or twice daily. A daily dose of 48 µg of eformoterol (corresponding to 36 µg delivered dose) should not be exceeded.

The dose can be administered in the morning and/or at night. The nightly dose can be taken to prevent awakening due to nocturnal asthma symptoms.

Prevention of Exercise-Induced Bronchospasm

One to two inhalations (6-12 µg eformoterol corresponding to 4.5 – 9 µg delivered dose) in the morning or before exercise.

Children 6 years of age and over

Paediatric and adolescent patients who require treatment with OXIS 6 TURBUHALER in addition to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and eformoterol to ensure compliance with both medications.

Regular Maintenance Dosing

If the use of OXIS 6 TURBUHALER is considered necessary, the recommended dosage for children six years of age and over is one to two inhalations (6 to 12 µg eformoterol, corresponding to 4.5 – 9 µg delivered dose) once or twice daily. A daily dose of 24 µg (corresponding to 18 µg delivered dose) of eformoterol should not be exceeded.

The dose can be administered in the morning and/or at night. The nightly dose can be taken to prevent awakening due to nocturnal asthma symptoms.

Prevention of Exercise-Induced Bronchospasm

One to two inhalations (6-12 µg eformoterol, corresponding to 4.5 – 9 µg delivered dose) in the morning or before exercise.

Children under 6 years of age

OXIS 6 TURBUHALER is not recommended for use in children under six years of age.

COPD

Adults

The normal dose is two inhalations (12 µg eformoterol, corresponding to 9 µg delivered dose) once or twice daily. Some patients may need up to four inhalations (24 µg, corresponding to 18 µg delivered dose) once or twice daily.

SPECIAL PATIENT GROUPS

No adjustment of dose should be required in elderly patients or in those with renal or hepatic impairment. However, no clinical studies have been performed in patients with renal or hepatic impairment.

METHOD OF ADMINISTRATION

OXIS 6 TURBUHALER is inspiratory flow driven, which means that, when the patient inhales through the mouthpiece, the substance will follow the inspired air into the airways.

NOTE: It is important to instruct the patient

- to carefully read the instructions for use in the patient information leaflet which are packed together with each inhaler
- to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is delivered to the lungs
- never to breathe out through the mouthpiece
- replace the cover of the OXIS 6 TURBUHALER after use.

The patient may not taste or feel any medication when using OXIS 6 TURBUHALER due to the small amount of medicine dispensed.

4.3 CONTRAINDICATIONS

The use of OXIS 6 TURBUHALER for the management of asthma is contraindicated without the use of an asthma controller medication such as an inhaled corticosteroid.

Hypersensitivity to eformoterol or to lactose.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The lowest effective dose of OXIS 6 TURBUHALER should be used.

For asthmatic patients, OXIS 6 TURBUHALER should only be used long-term where asthma symptoms cannot be adequately controlled using inhaled corticosteroids.

Anti-inflammatory therapy

OXIS 6 TURBUHALER should not be used (and is not sufficient) as initial treatment for asthma. It should only be prescribed when asthmatic patients continue to experience symptoms despite taking appropriate doses of inhaled anti-inflammatory therapy.

OXIS 6 TURBUHALER must not be prescribed as monotherapy to treat asthma.

Asthmatic patients who require therapy with a long-acting beta₂-agonist (LABA), should continue to receive optimal maintenance anti-inflammatory therapy with corticosteroids.

Patients must be advised not to stop or reduce corticosteroid therapy after the introduction of OXIS 6 TURBUHALER even when symptoms improve or if they feel better. Any change in corticosteroid dose should be made only after clinical evaluation.

For paediatric and adolescent patients who require treatment with a LABA, the use of a combination product containing an inhaled corticosteroid is recommended to ensure compliance with both medications.

The lowest effective dose of OXIS 6 TURBUHALER should be used. Once asthma symptoms are controlled, consideration may be given to stepping down treatment with OXIS 6 TURBUHALER. Regular review of patients as treatment is stepped down is important.

Acute asthma Symptoms

OXIS 6 TURBUHALER must not be used to relieve acute asthma symptoms. In the event of an acute attack, a short-acting bronchodilator should be used. Patients must be informed of this.

Deterioration of asthma control

Sudden and progressive deterioration of asthma control is potentially life threatening.

Increasing use of bronchodilators (in particular short-acting inhaled beta-2 agonists) to relieve symptoms indicates deterioration of asthma control. Patients must be informed of the need to seek medical treatment immediately if their asthma deteriorates suddenly, if they find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual.

In this situation, patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy.

Asthma exacerbations

Serious asthma-related adverse events and exacerbations may occur during treatment with OXIS 6 TURBUHALER. Patients should be asked to continue treatment but seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on OXIS 6 TURBUHALER.

OXIS 6 TURBUHALER must not be initiated or the dose increased during an asthma exacerbation. Severe exacerbations of asthma should be treated in the normal way with nebulised or parenteral bronchodilators and parenteral corticosteroids, together with other supportive measures.

Data from a large US study (The Salmeterol Multicenter Asthma Research Trial) comparing the safety of salmeterol (another LABA) with placebo, when added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol versus those receiving placebo (13 out of 13,176 vs 3 out of 13,179 over 28 weeks). Patients on salmeterol who did not receive inhaled corticosteroids as part of their usual therapy at the start of the study experienced a greater number of asthma-related deaths compared to those taking placebo (9 out of 7,049 vs. 0 out of 7,041). There were no significant differences between the salmeterol and placebo treatment groups among patients who were receiving inhaled corticosteroids at the start of the study.

Small clinical studies with eformoterol have suggested a higher incidence of serious worsening of asthma in patients who received eformoterol compared to placebo (see section 5.1 - Pharmacodynamic Properties).

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchospasm, OXIS 6 TURBUHALER should be discontinued immediately, the patient should be assessed, and an alternative therapy instituted if necessary. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway.

Use in patients with other medication OR conditions

Thyrotoxicosis

As for all beta₂-agonists, caution should be observed when treating patients with thyrotoxicosis.

Cardiovascular disorders

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. Therefore, OXIS 6 TURBUHALER should be used with caution in patients with pre-existing or with severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure.

QTc-interval prolongation

Caution should be observed when treating patients with prolongation of the QTc-interval. Eformoterol itself may induce prolongation of the QTc-interval.

Diabetes mellitus

OXIS 6 TURBUHALER should be administered with caution in patients with diabetes mellitus.

Due to the hyperglycaemic effects of beta₂-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Hypokalaemia

Potentially serious hypokalaemia may result from beta₂-agonist therapy. Particular caution is recommended in patients predisposed to low levels of serum potassium as well as those with severe asthma, as the associated risk may be augmented by hypoxia. Hypokalaemia may increase susceptibility to cardiac arrhythmias. The hypokalaemic effect may be potentiated by concomitant treatments (see section 4.5 - INTERACTIONS). Serum potassium levels should therefore be monitored in these patients.

Lactose Intolerance

OXIS 6 TURBUHALER contains lactose 895.5 micrograms/dose. This amount normally does not cause problems in lactose intolerant people.

Renal and Hepatic Impairment

The effect of decreased liver or kidney function on the pharmacokinetics of eformoterol is not known. As eformoterol is primarily eliminated via metabolism an increased exposure can be expected in patients with severe liver cirrhosis.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No specific interaction studies have been carried out with OXIS 6 TURBUHALER.

Beta-receptor blocking agents:

Beta-adrenergic blockers, especially those that are non-selective (including eye drops), can weaken or inhibit the effect of OXIS 6 TURBUHALER and may also increase airway resistance; therefore, the use of these medicines in asthma patients is not recommended.

Xanthine derivatives, mineralocorticosteroids and diuretics:

Hypokalaemia may result from β_2 -agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids, and diuretics, such as thiazides and loop diuretics (see section 4.4 Special Warnings and Precautions for Use).

Medicines affecting cardiovascular function

There is a theoretical risk that concomitant treatment with other medicines known to prolong the QTc-interval may give rise to a pharmacodynamic interaction with eformoterol and increase the possible risk of cardiovascular effects such as ventricular arrhythmias. Therefore, caution is advised when eformoterol is administered to patients already taking such medicines. Examples include certain antihistamines (terfenadine, astemizole, mizolastine), certain antiarrhythmics (e.g. quinidine, disopyramide, procainamide), erythromycin, phenothiazines and tricyclic antidepressants.

In addition, L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta₂-sympathomimetics.

Other sympathomimetic agents

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

4.6 FERTILITY, PREGNANCY AND LACTATION**Pregnancy**

Clinical experience in pregnant women is limited.

As with any medicine, use of OXIS 6 TURBUHALER during pregnancy should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus, especially during the first three months and shortly before delivery.

In animal studies, eformoterol 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 6 TURBUHALER.

Lactation

Eformoterol has been detected in small amounts in the milk of lactating rats; however, it is not known whether eformoterol passes into human breast milk. Administration of OXIS 6 TURBUHALER to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Fertility

Animal reproduction studies with formoterol have shown a somewhat reduced fertility in male rats at considerably higher systemic exposures than those reached during clinical use. Thus, these animal experimental results do not seem to be relevant in humans.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Oxis 6 TURBUHALER has no or negligible influence on the ability to drive or use machines.

4.8 UNDESIRABLE EFFECTS

Commonly reported adverse events are pharmacologically predictable side effects of beta-2-agonist therapy, such as tremor and palpitations. These tend to be mild and disappear within a few days of treatment.

Adverse events which have been associated with eformoterol are given below, listed by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1000$) and very rare ($< 1/10\ 000$).

Table 1 – Adverse Effects

Common	<i>Nervous system disorders</i>	Headache*, tremor, dizziness
	<i>Gastrointestinal disorders:</i>	Nausea
	<i>Musculoskeletal and connective tissue disorders</i>	Muscle cramps
Uncommon	<i>Cardiac disorders</i>	Tachycardia Palpitations Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles Angina pectoris
	<i>Psychiatric disorders</i>	Sleep disturbance
	<i>Immune system disorders</i>	Hypersensitivity reactions, e.g. bronchospasm, exanthema, urticaria, pruritis
	<i>Metabolism and nutritional disorders:</i>	Hypokalaemia, hyperglycaemia
	<i>Nervous system disorders</i>	Taste disturbance
	<i>Vascular disorders:</i>	Variations in blood pressure
	Rare	<i>Psychiatric disorders</i>

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

Treatment with beta₂-sympathomimetics may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 OVERDOSE

There is no clinical experience on the management of overdose.

Symptoms

An overdose of eformoterol would likely lead to effects that are typical of beta₂-adrenergic agonists and characteristic of excessive sympathetic stimulation: tremor, headache, palpitations and tachycardia. Hypotension, metabolic acidosis, hypokalaemia, hyperglycaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting may also occur.

Management

Supportive and symptomatic treatment may be indicated.

Beta-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: selective beta₂-agonist, formoterol, ATC code: R03A C13.

Mechanism of action and pharmacodynamics effects

Eformoterol is a potent, selective long-acting beta₂-agonist (LABA) which produces relaxation of bronchial smooth muscle. Eformoterol thus has a bronchodilating effect in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1 to 3 minutes after inhalation and has a mean duration of 12 hours after a single dose.

The addition of OXIS 6 TURBUHALER to inhaled corticosteroids has been proven in clinical trials to improve patient symptoms, reduce use of short acting reliever medication, reduce nocturnal awakenings, decrease the rate of exacerbations and improve quality of life.

Clinical efficacy and safety

In two, 12-week controlled trials with combined enrolment of 1095 patients with asthma 12 years of age and older, low and high dose eformoterol were compared with salbutamol and placebo. Serious asthma exacerbations (acute worsening of asthma resulting in hospitalisation) occurred more commonly in the high dose eformoterol group.

Table 2: Number and frequency of serious asthma exacerbations in patients 12 years of age and older from two 12 week controlled clinical studies

	Eformoterol (Foradil) 12 µg twice daily	Eformoterol (Foradil) 24 µg twice daily	Salbutamol 180 µg four times daily	Placebo
Trial #1				
Serious asthma exacerbations	0/136 (0%)	4/135 (3.0%) ¹	2/134 (1.5%)	0/136 (0%)
Trial #2				
Serious asthma exacerbations	1/139 (0.7%)	5/136 (3.7%) ²	0/138 (0%)	2/141 (1.4%)

- 1) 1 patient required intubation
- 2) 2 patients had respiratory arrest, 1 of the patients died

In a 16-week, randomised, multi-centre, double-blind, parallel-group trial of 1568 patients, eformoterol at the low and high doses was compared with placebo. Patients who received either 24 µg twice daily or 12 µg twice daily doses of eformoterol experienced more serious asthma exacerbations than patients who received placebo. There were no statistically significant differences between any groups.

Table 3: Number and frequency of serious asthma exacerbations in patients 12 years of age and older from a 16-week trial

	Eformoterol (Foradil) 12 µg twice daily	Eformoterol (Foradil) 24 µg twice daily	Placebo
Serious asthma exacerbations	3/527 (0.6%)	2/527 (0.4%)	1/514 (0.2%)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Inhaled eformoterol is rapidly absorbed and the peak plasma concentration is reached about 15 minutes after inhalation.

In a pharmacokinetic study, the mean lung deposition of eformoterol after inhalation via TURBUHALER was 43% of the delivered dose (corresponding to 32% of the metered dose). The total systemic availability was around 60% of the delivered dose.

Distribution and biotransformation

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

Elimination

The major part of the dose of eformoterol is eliminated via metabolism. After inhalation, 8 to 13% of the delivered dose of eformoterol is excreted unmetabolised in the urine. The terminal half-life after inhalation is estimated to be 8 hours.

5.3 PRECLINICAL SAFETY DATA

The effects of eformoterol seen in toxicity studies in rats and dogs were mainly on the cardiovascular system and consisted of hyperaemia, tachycardia, arrhythmias and myocardial lesions. These effects are known pharmacological manifestations seen after administration of high doses of beta₂-adrenoceptor agonists.

A somewhat reduced fertility in male rats was observed at high systemic exposure to eformoterol.

No genotoxic effects of eformoterol 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 beta₂-agonists.

6. PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**

Lactose monohydrate.

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF-LIFE

24 months

6.4 SPECIAL PRECAUTION FOR STORAGE

Store below 30°C with cover tightened.

6.5 NATURE AND CONTENTS OF CONTAINER

OXIS 6 TURBUHALER is a multidose, inspiratory flow driven, dry powder inhaler. The inhaler is made of plastic parts. Each inhaler contains 60 doses.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
P299 Private Bag 92175
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Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

7 May 1998

10. DATE OF REVISION OF TEXT

2 March 2017
(CDS 100615)

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Various	Change from M2 to M3 Turbuhaler Formatting changes in line with new SPC format.

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