PRODUCT MONOGRAPH

Pr OXEZE® TURBUHALER®

(formoterol fumarate dihydrate)

6 mcg/dose
and
12 mcg/dose

Dry Powder for Oral Inhalation

Bronchodilator

AstraZeneca Canada Inc.
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Pr OXEZE® TURBUHALER®

formoterol fumarate dihydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Turbuhaler/ 6 mcg/dose formoterol fumarate dihydrate 12 mcg/dose formoterol fumarate dihydrate	Lactose monohydrate (which may contain milk protein residue)

INDICATIONS AND CLINICAL USE

Asthma:

OXEZE TURBUHALER (formoterol fumarate dihydrate) is indicated for the treatment of asthma only as add-on therapy to an inhaled corticosteroid, a long-term asthma control medication, in patients 6 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.

Corticosteroids should not be stopped because formoterol is prescribed.

Formoterol is a long-acting $beta_2$ agonist (LABA) and should not be used as a rescue medication. To relieve acute asthmatic symptoms a short-action inhaled bronchodilator should be used.

LABA, such as formoterol, the active ingredient in OXEZE, may increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). Use of OXEZE for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated (see CONTRAINDICATIONS). Use OXEZE only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals and consider stepping down therapy (e.g. discontinue OXEZE) if possible without the loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use OXEZE for patients whose asthma is adequately controlled on low- to medium-dose inhaled corticosteroids.

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients (see WARNINGS AND PRECAUTIONS). For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

Exercise-Induced Bronchoconstriction:

OXEZE is also indicated for the acute prevention of exercise-induced bronchoconstriction in adults and children 6 years of age and older, when administered on an occasional, as-needed basis. OXEZE may be clinically indicated as a single agent for the prevention of exercise-induced bronchoconstriction in patients who do not have persistent asthma. In patients with persistent asthma, use of OXEZE for the prevention of exercise-induced bronchoconstriction should only be considered if the treatment of asthma includes a long-term asthma control medication, such as an inhaled corticosteroid (see CONTRADICTIONS).

CONTRAINDICATIONS

OXEZE TURBUHALER (formoterol fumarate dihydrate) is contraindicated when there is known hypersensitivity to formoterol or inhaled lactose. Like other sympathomimetic amines, OXEZE TURBUHALER should not be used in patients with tachyarrhythmias.

Because of the potential risk of death and hospitalization, use of OXEZE for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

WARNING FOR ASTHMA PATIENTS

Asthma-Related Death: Long-acting beta$_2$ agonists (LABA), such as formoterol, the active ingredient in OXEZE, may increase the risk of asthma-related death. Data from a large placebo-controlled US study, which compared the safety of salmeterol, a LABA, with placebo when added to patients' usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a LABA class effect. Currently available data are inadequate to determine whether concurrent use of inhaled

corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Because of this potential risk, use of OXEZE for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated (see CONTRAINDICATIONS). Use OXEZE only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and consider stepping down therapy (e.g. discontinue OXEZE) if possible without the loss of asthma control. Patients should be maintained on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use OXEZE for patients whose asthma is adequately controlled on low- to medium-dose inhaled corticosteroids (see DOSAGE AND ADMINISTRATION).

Pediatric and Adolescent Patients:

Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate inhaled corticosteroid and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended (see DOSAGE AND ADMINISTRATION).

General

Use of Anti-Inflammatory Agents

Patients should be receiving optimal anti-inflammatory therapy with corticosteroids before starting maintenance treatment with OXEZE TURBUHALER. Formoterol is not a substitute for inhaled or oral corticosteroids; its use is complementary to them. Corticosteroids should not be stopped when OXEZE TURBUHALER is initiated. Patients must be advised not to stop or reduce corticosteroid therapy without medical advice (see CONTRAINDICATIONS).

OXEZE TURBUHALER and the Management of Asthma

OXEZE TURBUHALER may be used as a regular twice daily maintenance regimen. The management of asthma should normally follow a stepwise programme, as advised in asthma management guidelines, with patient response monitored clinically and by lung function tests. The lowest effective dose of OXEZE TURBUHALER should be used.

Consideration should be given to the following in the management of asthma with OXEZE TURBUHALER:

- Use of OXEZE for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated.

- Adequate education should be provided to the patient regarding the use of long-acting β_2-agonists.

- Increasing use of OXEZE TURBUHALER or other fast-acting bronchodilators to control symptoms indicates deterioration of asthma control and the need to reassess the patient's therapy.

Sudden or progressive deterioration in asthma control is potentially life-threatening; the treatment plan must be re-evaluated, and consideration be given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring with precise instructions for acceptable variation limits should be considered.

Watch for Increased Need for Rescue Medication

Fast-acting, inhaled bronchodilators (e.g., terbutaline, salbutamol) may be used for relief of breakthrough symptoms. Asthma may deteriorate acutely over a period of hours or slowly over several days or longer. **The total maximum daily dose of OXEZE TURBUHALER should not be exceeded.** Should symptoms persist, or treatment with fast-acting inhaled β_2-agonist become less effective or a patient needs more inhalations than usual, this indicates a worsening of the underlying condition and warrants reassessment of the treatment regimen and consideration given to increasing corticosteroid therapy. Patients requiring increasing doses or inhalations of fast-acting β_2-agonists for relief of symptoms should be advised to consult a physician for re-evaluation. In the case of acutely or rapidly worsening dyspnea, a doctor should be consulted immediately.

Do Not Exceed Recommended Dosage

OXEZE TURBUHALER should NOT be used at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs (see below).

Cardiovascular

Potentially serious ECG changes (such as increased QTc interval) and hypokalemia may result from β_2-agonist therapy. Although clinically not significant, a small increase in QTc interval and/or decrease in serum potassium has been reported at therapeutic doses of formoterol. Particular caution is advised in severe asthma as these effects may be potentiated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics. Hypokalemia will increase the susceptibility of digitalis patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations. Therefore, OXEZE TURBUHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, arrhythmias and hypertension.

Usually no effect on the cardiovascular or central nervous system is seen after the administration of formoterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased heart rate, cardiac contractility, tremor) can occur while using formoterol. Special care and supervision,

with particular emphasis on dosage limits, is required in patients with the following conditions receiving OXEZE TURBUHALER: ischemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, severe hypertension, hypertrophic obstructive cardiomyopathy, thyrotoxicosis or severe heart failure.

Use with caution in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Caution should be observed when treating patients with known or suspected prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

Endocrine and Metabolism

Sympathomimetic bronchodilators should be administered cautiously to patients who are unusually responsive to sympathomimetic amines, e.g., in patients with hyperthyroidism not yet under adequate control. Since β_2-agonists may increase the blood glucose level, additional blood glucose controls are recommended when asthmatic patients with concomitant diabetes are started on OXEZE TURBUHALER.

Respiratory

Paradoxical Bronchospasm: As with other inhaled asthma medication, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, treatment with OXEZE TURBUHALER should be discontinued immediately and alternative therapy instituted.

Sensitivity/Resistance

Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of OXEZE TURBUHALER. OXEZE TURBUHALER contains lactose (approximately 1000 mcg per dose) and is contraindicated in patients with hypersensitivity to inhaled lactose or formoterol. The amount of lactose in OXEZE TURBUHALER does not normally cause problems in lactose intolerant people (see CONTRAINDICATIONS).

Special Populations

Pregnant Women: The safety of formoterol during pregnancy has not yet been established. OXEZE TURBUHALER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no well-controlled human studies that have investigated the effects of formoterol on preterm labour or labour at term. Because of the potential for β-agonist interference with uterine contractility, use of β_2-agonists, such as OXEZE TURBUHALER, during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Women: Formoterol was found to be excreted in the milk of lactating rats after oral administration. Since there is no experience in the use of OXEZE TURBUHALER in nursing mothers, its use in such circumstances should only be considered if the expected benefit to the mother is greater than the risk to the infant.

Pediatrics: OXEZE TURBUHALER is not recommended for children younger than 6 years of age due to limited clinical data in this age group.

In children and adolescents the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued therapy with OXEZE TURBUHALER is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of rescue medication, should be carefully followed in this age group.

Geriatrics: No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment, at the recommended normal doses. (See also WARNINGS and PRECAUTIONS for patients with cardiovascular disorders).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

OXEZE TURBUHALER (formoterol fumarate dihydrate) has been used by more than 29,000 patients in clinical trials. The total post marketing exposure to OXEZE TURBUHALER is more than 2.4 million treatment-years. The most commonly reported adverse symptoms, which constitute the majority of the reports, are listed as adverse side effects of β_2-agonist therapy. There has been no indication of any particularly serious or unanticipated drug related reactions. The frequencies listed below are from the pooled placebo controlled clinical trials. Pharmacologically predictable side-effects of β_2-agonist therapy, such as tremor and palpitations, may occur but tend to be transient and reduced with regular therapy. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. The following adverse reactions can be classified as common (i.e. frequency $\geq$ 1% and <10%): tremor, headache, dizziness, nausea and muscle cramps; uncommon (frequency $\geq$ 0.1% and <1%): tachycardia, palpitations, cardiac arrythmias (e.g., atrial fibrillation, supraventricular tachycardia, extrasystoles), angina pectoris, sleep disturbances, hypersensitivity reaction (e.g., bronchospasm, exanthema, urticaria, pruritus), hypokalemia, hyperglycemia, taste disturbance and variations in blood pressure; rare (frequency $\geq$ 0.01% and < 0.1%): agitation and restlessness.

Long-acting beta$_2$ agonists (LABA), including formoterol, the active ingredient in OXEZE, may increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatrics and adolescent patients (WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

The incidence of adverse events, irrespective of causality towards the drug, from four controlled trials (duration 1, 3, 3 and 6 months, respectively) with OXEZE TURBUHALER is presented in the following table.

Table 1 **Incidence Of Adverse Events (Irrespective Of Causality) With Frequency Higher Than Placebo In Four Controlled Trials Of Duration 1, 3, 3 And 6 Months Respectively.**

	OXEZE TURBUHALER			Placebo TURBUHALER
	Total	6 mcg b.i.d.	12 mcg b.i.d.	
	No. (%)	No. (%)	No. (%)	No. (%)
Total Number of Evaluable Patients	359	190	169	412
Headache	66 (18%)	15 (8%)	51 (30%)	84 (20%)
Tremor	11 (3%)	4 (2%)	7 (4%)	2 (0%)
Pharynx Disorder	18 (5%)	3 (2%)	15 (9%)	10 (2%)
Cramps	10 (3%)	3 (2%)	7 (4%)	3 (1%)

Post-market Adverse Drug Reactions

The following adverse reactions have been reported during post-approval use of OXEZE. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Some of these adverse reactions may also have been observed in clinical studies with OXEZE

Cardiac disorders: angina pectoris, tachycardia, cardiac arrhythmias (e.g. atrial fibrillation, extrasystoles), palpitations

Gastrointestinal disorders: nausea

Immune system disorders: brochospasm, urticaria, rash, dermatitis, pruritus

Metabolic and nutrition disorders: hyperglycemia, hypokalemia

Musculoskeletal, connective tissue, and bone disorders: muscle spasms

Nervous system disorders: tremor, dizziness, headache

Psychiatric disorders: behaviour disturbances, sleep disturbances, nervousness, agitation, restlessness

Vascular disorders: variations in blood pressure, hypertension

DRUG INTERACTIONS

Beta-Receptor Blocking Agents

Beta-receptor blocking agents (including eye drops), especially non-selective ones, may partly or totally inhibit the effect of beta-stimulants.

Should a patient treated with OXEZE TURBUHALER (formoterol fumarate dihydrate) also require concomitant treatment with a beta-blocker, it is recommended that a beta-blocker (e.g., metoprolol) with less predominant β_2-blocking effects be considered. If concomitant treatment is necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug.

Xanthine Derivatives, Steroids and Diuretics

Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalemic effect of β_2-agonists. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Other Drugs

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is elevated risk of arrhythmias in patients receiving concomitant anesthesia with halogenated hydrocarbons.

DOSAGE AND ADMINISTRATION

Dosing Considerations for Asthma:

Long-acting beta$_2$ agonists (LABA), such as formoterol, the active ingredient in OXEZE, may increase the risk of asthma-related death (see WARNINGS AND PRECAUTIONS). Because of this potential risk, use of OXEZE for the treatment of asthma without concomitant use of an inhaled corticosteroid, a long-term asthma control medication, is contraindicated (see CONTRAINDICATION). Use OXEZE only as add-on therapy for patients with asthma who are currently taking but are inadequately controlled on an inhaled corticosteroid.

Once asthma control is achieved and maintained, assess the patient at regular intervals and consider stepping down therapy (e.g. discontinue OXEZE) if possible without loss of asthma control. Patients should be maintained on a long-term asthma control medication, such as an

inhaled corticosteroid. Do not use OXEZE for patients whose asthma is adequately controlled on low- to medium-dose inhaled corticosteroids (see WARNINGS and PRECAUTIONS).

Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g. inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended (see WARNINGS AND PRECAUTIONS).

OXEZE TURBUHALER SHOULD NOT BE USED AT HIGHER DOSES THAN RECOMMENDED. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's fast-acting inhaled β_2-agonist becomes less effective or a patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reassessment of the treatment regimen. Increasing the daily dosage of OXEZE TURBUHALER in this situation is not appropriate (see WARNINGS AND PRECAUTIONS).

Bronchodilators should not be the only or the main treatment in patients with moderate to severe or unstable asthma. Patients with severe asthma may require regular medical assessment. These patients will require high dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under medical supervision.

Recommended Dose and Dosage Adjustment

Since there may be serious adverse effects associated with excessive dosing, the dosage should not be increased beyond the maximum recommended dose. Dosage should be individualized and patient response should be monitored by the prescribing physician on an ongoing basis.

1. Asthma

As a twice daily regular treatment, OXEZE TURBUHALER provides 24-hour bronchodilation when used concurrently with corticosteroid therapy.

The dose of OXEZE TURBUHALER should be individualized to the patient’s needs and should be the lowest possible dose that keeps the patient symptom free or fulfils the therapeutic objective.

Adults: The usual dose is 6 or 12 mcg from OXEZE TURBUHALER, twice daily, at 12 hour intervals. Some patients may need 24 mcg twice daily. In adults, the maximum recommended daily dose is 48 mcg.

Children (6-16 years): The usual dose is 6 or 12 mcg, twice daily, at 12 hour intervals. In children, the maximum recommended daily dose is 24 mcg.

In children and adolescents, the severity of asthma may be variable with age and periodic reassessment should be considered to identify the lowest dose required to maintain control and to determine if continued maintenance therapy with OXEZE TURBUHALER is still indicated (see WARNINGS AND PRECAUTIONS).

OXEZE TURBUHALER is available in two strengths, 6 or 12 mcg per inhalation. Use of the higher strength is recommended for patients requiring 12 mcg or more, twice daily.

OXEZE TURBUHALER should not be used to relieve the acute symptoms of an asthma attack. In the event of an acute attack, a short-acting beta$_2$-agonist should be used.

OXEZE TURBUHALER is not recommended for children younger than 6 years of age due to limited clinical data in this age group.

2. Prevention of Exercise-Induced Bronchoconstriction

Adults and Children 6 years of age and older: 6 or 12 mcg before exercise.

When OXEZE TURBUHALER is used to prevent exercise-induced bronchoconstriction, the maximum dose during a 24 hour period should not exceed 48 mcg in adults and 24 mcg in adolescents and children.

OXEZE may be clinically indicated as a single agent for the prevention of exercise-induced bronchoconstriction in patients who do not have persistent asthma. In patients with persistent asthma, use of OXEZE for the prevention of exercise-induced bronchoconstriction should only be considered if the treatment of asthma includes a long-term asthma control medication, such as an inhaled corticosteroid (see CONTRAINDICATIONS).

NOTES: The medication from OXEZE TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication when using OXEZE TURBUHALER due to the small amount of drug dispensed.

It is important to instruct patients to avoid exhaling into the device and to always replace the cover after using OXEZE TURBUHALER.

Missed Dose

If a dose of twice daily maintenance treatment of OXEZE TURBUHALER is missed, it should be taken as soon as possible within 6 hours of the missed dose; the patient should then resume their regular schedule. If more than 6 hours have passed, the missed dose should not be taken. Patients should be advised to take their next scheduled dose on time.

A double dose of OXEZE TURBUHALER should never be taken to make up for missed doses.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

There is limited clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of β_2-adrenergic agonists: tremor, headache, palpitations. Metabolic acidosis and hypertension may also occur. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient in OXEZE TURBUHALER (formoterol fumarate dihydrate), formoterol, produces bronchodilation by stimulation of the β_2 adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of smooth muscle fibres.

Pharmacodynamics

Following inhalation from OXEZE TURBUHALER (formoterol fumarate dihydrate), a marked improvement in pulmonary function is observed within 1-3 minutes. This fast onset of action is similar to that seen with short-acting bronchodilators (e.g., terbutaline, salbutamol). Approximately 80% of peak effect is attained within 15 minutes of administration. In addition, formoterol has a mean duration of bronchodilator effect of 12 hours after a single dose, much like other long-acting β_2-agonists.

Pharmacokinetics

Absorption: Inhaled formoterol is rapidly absorbed. Peak plasma concentration is reached about 15 minutes after inhalation.

In a pharmacokinetic study, the mean lung deposition of formoterol 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: Plasma protein binding is approximately 50%.

Metabolism: Formoterol is metabolized 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.

Excretion: The major part of the dose of formoterol is eliminated via metabolism. After inhalation 6-10% of the dose of formoterol is excreted unmetabolized 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 8 hours.

STORAGE AND STABILITY

OXEZE TURBUHALER (formoterol fumarate dihydrate) should be stored at room temperature between 15°C and 30°C with the cover tightened.

SPECIAL HANDLING INSTRUCTIONS

OXEZE TURBUHALER (formoterol fumarate dihydrate) cannot be refilled and should be discarded when empty.

DOSAGE FORMS, COMPOSITION AND PACKAGING

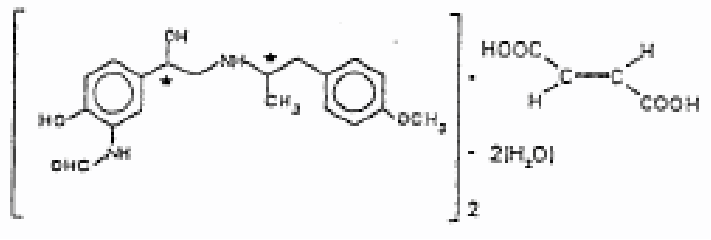
OXEZE TURBUHALER (formoterol fumarate dihydrate) is supplied in two strengths: 6 mcg/dose (60 doses) and 12 mcg/dose (60 doses). This corresponds to a delivered dose (the dose leaving the mouthpiece) of 4.5 mcg or 9 mcg formoterol fumarate dihydrate, respectively.

OXEZE TURBUHALER also contains lactose (approximately 1000 mcg per dose). This amount does not normally cause problems in lactose-intolerant people.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name	formoterol fumarate dihydrate
Chemical Name	(R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide, (E)-2-butendioate(2:1), dihydrate
Molecular Formula and Molecular Mass	$C_{42}H_{56}N_4O_{14}$ 840.9
Structural Formula	
Physicochemical Properties	Formoterol fumarate dihydrate is a white to off-white or slightly yellow non-hygroscopic crystalline powder.
Dissociation Constant	The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.
Partition Coefficient	The octanol-water partition coefficient at 25°C is 2.6.

DETAILED PHARMACOLOGY

Human Pharmacology

Absorption and Bioavailability

Inhaled formoterol reaches the systemic circulation via two routes, absorption in the lungs (pulmonary bioavailability) and absorption in the gut (oral bioavailability). Inhaled formoterol is rapidly absorbed and the peak plasma concentration is reached about 15 minutes after inhalation. The mean pulmonary bioavailability has been estimated in a pharmacokinetic study to be 43% of the delivered dose (corresponding to 32% of the metered dose). The total systemic availability after inhalation is approximately 60% of the delivered dose.

Distribution and Metabolism

Plasma protein binding is approximately 50%. Formoterol is metabolized via direct glucuronidation and O-demethylation. Direct conjugation of formoterol, and phase 1

biotransformation followed by conjugation, are likely metabolic fates of formoterol. The oxidative metabolism is likely to be slower in cirrhotic patients, but, conjugation capacity should essentially be maintained since glucuronidation appears to be little affected in conjunction with cirrhosis. Thus, cirrhosis should not *a priori* be expected to reduce the capacity to eliminate formoterol. If, however, metabolic clearance really were reduced, the increase in plasma concentrations after inhalation should not hinder the use of clinically recommended doses of OXEZE TURBUHALER (formoterol fumarate dihydrate) (6-12 mcg b.i.d.) even with a 50% reduction in total clearance.

Elimination

The major part of the dose of formoterol is eliminated via metabolism. After inhalation 6-10% of the dose of formoterol is excreted unmetabolized in the urine. Following i.v. infusion of formoterol, about 19% of the dose was excreted in urine as unmetabolized formoterol within 24-48 hours. Less than 10% of the nominal dose was recovered intact after inhalation without concomitant charcoal. A considerable fraction of the dose might be excreted in urine as metabolite(s) of formoterol (e.g., Met1), or as conjugates of these metabolite(s).

The terminal half-life after inhalation is estimated to be around 8 hours.

Pharmacodynamics

A dose-response relationship was evident when single doses of OXEZE TURBUHALER were investigated within the dose range of 3 to 48 mcg. Compared with placebo, all tested doses resulted in statistically significant increases in mean FEV_1 values, however, the maximum increase after 3 mcg was not significantly different from placebo. As the maximum effect on FEV_1 and the duration of efficacy are important measures of clinical efficacy, the 3 mcg dose was considered a clinically less appropriate dose, especially as the tolerability of the higher doses was good. The 6 mcg dose was thus defined as the lowest effective dose. OXEZE TURBUHALER has an onset of action (1 to 3 minutes) similar to that seen with short-acting inhaled β_2-agonists and faster than that with salmeterol. Single doses of 6, 12, 24 and 48 mcg OXEZE TURBUHALER result in l2-hour duration of bronchodilation. The duration is dose-dependent and the duration for 12 mcg OXEZE TURBUHALER is similar to that of 50 mcg salmeterol.

A dose-dependent tremor of mild or moderate intensity was observed in healthy subjects not earlier exposed to OXEZE TURBUHALER.

OXEZE TURBUHALER in doses up to and including 48 mcg did not statistically significantly increase the pulse rate, neither in healthy subjects nor in asthmatics as compared with placebo. A clinically relevant increase in pulse rate was observed in healthy subjects after a cumulative dose of 72 mcg of OXEZE TURBUHALER.

When a cumulative dose of 72 mcg OXEZE TURBUHALER was given to healthy subjects, statistically significant but clinically not important increases in systolic and decreases diastolic blood pressure were found. No important changes were found when blood pressure was

monitored in patients with asthma receiving single doses or repeated daily doses of 48 mcg of OXEZE TURBUHALER.

An expected dose-response relationship has been documented for the prolongation of the QTc time, with a single dose of 24 mcg in healthy subjects being significantly different from placebo. However, the absolute changes seen even after cumulative dose of 72 mcg OXEZE TURBUHALER in healthy subjects cannot be considered clinically important. It should be noted that the QTc time may not be the best measure of cardiac effects. The QTc time may even be misleading when QT intervals and heart rate change at the same time.

An initial decrease in $S\text{-}K^+$ was noted in healthy subjects after administration of OXEZE TURBUHALER but a rapid tolerance to the hypokalemic effect was noted. No clinically significant decreases in $S\text{-}K^+$ were reported in studies in patients with asthma. No hypokalemic tendency was noted in the OXEZE TURBUHALER long-term studies.

A high cumulative dose of OXEZE TURBUHALER was associated with statistically significant, but clinically not important increases in plasma glucose and lactate in healthy subjects.

TOXICOLOGY

Acute Toxicity

The acute toxicity of formoterol was studied in mice and rats after inhalation and oral administration. The inhalation LD_{50} values in mice and rats were estimated to be >280 mg/kg and 40-200 mg/kg respectively. The oral LD_{50} values were estimated to be in the range of >2000 mg/kg in adult mice and rats, and 500-1000 mg/kg in young rats (12-14 days old). Symptoms of acute toxicity were decreased motor activity, abdominal respiration, tremor, increased salivation and chromodacryorrhea. Myocardial lesions were found in some severely affected animals. This is an expected finding with a high dose of β-adrenoceptor stimulating agents such as isoprenaline, salbutamol and terbutaline.

The effects noted in the single dose studies are those which can be expected with a potent β-agonist.

Long Term Toxicity

The general toxicity after repeated administration of formoterol was studied in mice, rats and dogs after inhalation and oral administration. Studies in young rats were also performed.

Table 2 **Dose Levels In Repeat Dose Toxicity Studies And Exposure Ratios Animal/Man* Of Mean C_{max} And AUC For Unchanged Formoterol.**

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/Man)		Results and Observations
			C_{max}	AUC	
Mouse	p.o. 3 months	0.1 1.0 10.0	<2.2 37 >343	n.c. 25 214	- slight increase in serum urea (dose-dependent) - minor decrease in adrenal weights (medium - high dose) - increased respiratory frequency, decreased motor activity, increased salivation and signs of cyanosis (gradually appearing in high dose; most pronounced in males) - increase in body weight (high dose females) - slight decrease in serum phosphate (high dose) - slight increase in serum ALT activity (high dose) - minor increase in spleen and liver weights (high dose females)
Rat	inhal 5 days	0.12 0.80 3.7	- - -	- - -	- increase in body weight gain - increase in heart weight (females) - solitary histopathological microfocal leukocyte foci in the heart (2 high dose males of 6)
	inhal 3 months	0.082 0.26 0.87	60 163 341	63 108 215	- tachycardia - slight increase in PCV, Hb and number of RBC (females) - reduction in platelet count (dose-dependent in males) - decrease in blood glucose (dose-dependent) - increase in heart weight (more pronounced in females) - increase in PCV (medium - high dose males) - slight increase in serum urea (medium - high dose) - increase in serum ALT activity (medium - high dose males) - increased body weight gain (high dose females)

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/Man)		Results and Observations
			C_{max}	AUC	
	inhal 6 months	0.026 0.13 0.85	16 63 278	18 68 264	- tachycardia - slight increase in Hb, hematocrit and/or number of RBC (females) - slight reduction in platelet count - increase in serum urea (dose-dependent in males) - decrease in blood glucose (possibly dose dependent in females) - small increase in serum ALT activity - slight increase in serum potassium (more pronounced in females) - increase in urine volume - slight decrease in urine osmolality (low - medium dose females) - slight increase in urinary pH - increase in heart weight - minimal histopathological reactive changes in lungs and nasal cavity - increased food consumption (medium - high dose) - slight decrease in thymus weight (medium - high dose) - minimal histopathological foci of myocardial fibrosis (medium - high dose) - increase in body weight gain (high dose females)

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/Man)		Results and Observations
			C_{max}	AUC	
Young rat	p.o. 3 months original study	0.2 0.8 3	≥3.3 8.1 29	n.c. 17 60	- slight increase in total leukocyte count - slight increase in serum urea (dose-dependent in females) - decrease in blood-glucose (dose-dependent in females) - increase in serum potassium - testicular atrophy (not dose-dependent; also found in control animals) - increase in heart weight (medium - high dose males) - minimal histopathological foci of myocardial changes (medium dose males; high dose both sexes) - slight increase in serum ALT activity (high dose males) - decrease in testis weight (high dose)
Young rat cont.	p.o. 3 months repeat study in males	0.03 0.2 0.8 3	- - 9.8 37	- - 15 56	- testicular findings in original study not reproducible - decreased water consumption - increased incidence of hyperemic scrotum and distinctly visible testes (also with salbutamol) - increase in body temperature - increase in lung and spleen weights (medium - high dose) - increased food consumption (high dose) - increase in heart weight (high dose)

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/Man)		Results and Observations
			C_{max}	AUC	
	inhal 3 months	0.028 0.16 0.78	18 97 380	15 82 291	- tachycardia - increase in total leukocyte count - slight decrease in blood glucose (females) - increase in body weight gain (medium - high dose males) - increase in food consumption (medium - high dose males) - slight increase in the number of RBC (medium - high dose females) - increase in heart weight (medium - high dose) - slight increase in Hb (high dose females)
Dog	inhal 5 days	0.0005 0.0029 0.015	1.7 6.3 48	n.c. 5.3 44	- hyperemia of the mucosa and abdominal skin - tachycardia - slight non-dose-dependent decrease in Hb, hematocrit and number of RBC - chronic bronchopneumonia (males; not caused by but possibly exacerbated by treatment) - hyperventilation and cough (high dose males) - slight to moderate foci of myocardionecrosis/fibrosis (high dose)
	inhal 1 month	0.0005 0.0029 0.015	1.8 6.2 51	n.c. 6.4 44	- slight body weight increase (dose-dependent) - tachycardia related to drug administration - slight (low - medium dose) to moderate (high dose) histopathological foci of myocardial fibrosis - hyperemia of the mucosa and abdominal skin (dose-dependent) - slight decrease in Hb, hematocrit and number of RBC (medium - high dose) - ventricular arrhythmias in some individuals (1 of 6 medium dose and 3 of 6 high dose males)

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/Man)		Results and Observations
			C_{max}	AUC	
	p.o. 1 month	0.002 0.015 0.1	3.9 25 98	n.c. 29 217	- tachycardia - hyperemia of the mucosa and abdominal skin - slight non-dose-dependent increase in serum urea and creatinine - bilateral periorbital edema (medium - high dose) - occasional ventricular arrhythmia (1 medium dose animal of 6 and 3 high dose animals of 6) - slight decrease in urinary pH - occasional laboured respiration (high dose) - slight decrease in heart, spleen, kidneys, testes, prostate and epididymis weights (high dose males) - treatment-related moderate foci of myocardial fibrosis (4 high dose animals of 6)
	p.o. 12 months	0.0007 0.0086 0.092	1.4 17 131	n.c. 24 265	- hyperemia of the mucosa and abdominal skin (dose-dependent) - transient discoloration of the claw keratin (dose-related) - tachycardia - slight non-dose-dependent increase in serum urea and creatinine - papillary myocardial fibrosis (dose-dependent; 2 low, 3 medium and 5 high dose animals of 10) - ventricular ectopic extrasystole (1 medium dose female, 3 high dose females and 4 high dose males of 5) - slight decrease in Hb and hematocrit (medium - high dose) - slight increase in serum potassium (high dose) - slight increase in blood glucose (high dose males) - slight increase in serum ALT activity (high dose females)

n.c. = not calculable * Based on a human dose of 24 mcg.

The effects observed in the repeat dose toxicity studies in mice, rats and dogs are those which can be expected with a potent β_2-agonist. The most prominent are those on the cardiovascular system with tachycardia, ventricular arrhythmia and myocardial lesions at high doses. In some studies slightly elevated serum potassium was noted, which is contrary to what is usually seen clinically, i.e., reduced serum potassium after acute exposure to a β_2-agonist. In this context it should be mentioned that blood sampling for clinical chemistry in toxicological studies is routinely performed about 24 hours after dosing. Thus, the slightly elevated serum potassium may be due to a rebound effect. The same explanation may also be valid for other discrepancies between clinical and toxicity studies, e.g., blood glucose variations. A slight elevation of ALT activity was noted in some of the studies which may indicate effects on the liver although no morphological changes were found.

The findings of an increased incidence of testicular atrophy noted in the original study in young rats with formoterol was not reproducible. All other repeat dose studies performed with formoterol in mice, rats and dogs (adult animals) have been reviewed with regard to testicular atrophy. There is no evidence from these studies that formoterol causes testicular atrophy. It is concluded that the testicular effects noted in the first study in young rats are equivocal in nature and are therefore considered to be of no relevance in the clinical setting.

Mutagenicity

The mutagenic potential of formoterol was studied in the Ames test, Mouse Lymphoma L5178 TK +/- assay, *in vitro* chromosome aberration test in human lymphocytes and the rat micronucleus test. In the Ames test two batches of formoterol were each tested in two independent experiments. A weak but significant increase in the number of revertant colonies was seen in one of the experiments using each batch. However, since the mutagenic effects were neither reproducible nor dose related, it was concluded that formoterol was not mutagenic in this test. Neither was it mutagenic at the thymidine kinase locus in L5178Y mouse lymphoma cells, nor did it not induce chromosome aberrations in human lymphocytes *in vitro* or micronuclei in rats treated with formoterol by inhalation. Considering that the mouse lymphoma and chromosome aberration tests are generally more sensitive than the Ames test, and the low and inconsistent activity seen in the two different Ames tests, it was concluded that formoterol is not an *in vitro* mutagen. The negative results in the micro-nucleus test indicated that the compound is not mutagenic *in vivo* either.

Carcinogenicity

The carcinogenic potential of formoterol was studied in mice after oral administration and in rats after inhalation. The only treatment related findings were increased incidence of uterine leiomyomas in mice and one mesovarian leiomyoma in rats. These are expected findings in rodents with β-stimulating agents.

Table 3 Dose Levels Carcinogenicity Studies And Exposure Ratios Animal/Man* Of Mean C_{max} And AUC For Unchanged Formoterol

Species	Route Duration	Dose mg/kg	Exposure Ratio (Animal/man)		Results and Observations
			C_{max}	AUC	
Mouse	p.o.	0.1	5.6	n.c.	-dose-related increased incidence of uterine leiomyomas
	24 months	0.5	8.9	6.4	-dose-related increased incidence of uterine leiomyomas
		2.5	59	56	-dose-related increased incidence of uterine leiomyomas
Rat	inhal	0.005	4.8	n.c.	
	24 months	0.022	17	15	
		0.13	67	66	-single mesovarian leiomyoma found, considered to be dose-related

n.c. = not calculable * Based on a human dose of 24 mcg.

Reproductive Studies

A complete program of reproduction toxicology studies was performed in rats and rabbits. In these studies formoterol was administered either orally or by inhalation.

In the fertility study in rats with formoterol given orally by gavage, a reduction in male fertility (fertility 78% of control) was noted at the high dose level (15 mg/kg) in the main study. This effect was not seen at the mid (3 mg/kg) or low (0.2 mg/kg) dose levels. This reduction in fertility was associated with a slight decrease in testes weight at the high dose level, although not statistically significant. Histological examination of the testes did not reveal an increased incidence or severity of testicular atrophy at the high dose level or any other dose level in comparison with the control group. The overall incidence of testicular atrophy in this study was within the historical control data of this laboratory. That male, but not female fertility was affected was indicated by the finding that formoterol treated satellite group females, who were mated with untreated males, showed a 100% pregnancy rate, even in the 15 mg/kg dose group. It was noted that untreated females mated with males from the 15 mg/kg dose group (male's second mate) showed reduced fertility (81% of control). At the high dose level, 15 mg/kg, the systemic exposure (C_{max} and AUC) was about 1300 times the recommended human exposure.

Effects upon pregnancy were studied in rats after inhalation of formoterol (dose range 0.004-1.2 mg/kg). The maternal body weight was dose-dependently increased versus the control from the beginning of the dosing period. Dose related tachycardia was also noted. Mean placental weights were statistically significantly increased in all dose groups compared with the control group.

No adverse effects which could be related to the treatment with formoterol on organogenesis or fetal development were noted up to and including 1.2 mg/kg (high dose level).

Effects upon pregnancy were also studied in rabbits after oral gavage at doses of 0.2, 3.5 and 60 mg/kg. Increased maternal weight gain was observed at all dose levels, most notably at 60 mg/kg. A slight increase in placental weight and a higher proportion of fetuses with subcapsular liver cysts were also noted at 60 mg/kg. The percentage of fetuses with extra ribs and reduced and/or asymmetric/bipartite sternebrae at this dose level was also higher although considered to be of uncertain treatment relationship.

There was no clear adverse effect of treatment on embryonal development at 0.2 or 3.5 mg/kg. At the high dose level systemic exposure (C_{max} and AUC) was about 7000-11000 times the recommended human exposure.

As to possible effects on late pregnancy, delivery and offspring development rats were treated orally by gavage with formoterol in the dose range 0.2-3.4 mg/kg. A dose-dependent increase in maternal body weight gain was noted. The number of non-pregnant females and females with total litter loss was slightly higher in the mid (0.8 mg/kg) and the high dosed groups (3.4 mg/kg). The litter weights and the mean pup weights were slightly reduced in the dose groups, but with no obvious dose dependency. There were no differences in the developmental milestones, the reflex development or the functional tests. No differences in sexual function or fertility between groups were seen (F1 generation).

No serious adverse effects on reproduction were noted. The most important finding is a reduced fertility at the high dose level (about 1300 times higher than maximal recommended human systemic exposure) in the rat. Thus, it is considered that it does not represent a clinical problem.

REFERENCES

1. Anderson GP.
Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β_2-adrenoceptor agonist bronchodilator. Life Sci 1993;52:2145-2160.

2. Decker N, Quennedey MC, Rouot B, Schwartz J, Velly J.
Effects of N-aralkyl substitution of β-agonists on α- and β-adrenoceptor subtypes: Pharmacological studies and binding assays. J Pharm Pharmacol 1982;34:107-112.

3. Derom EY, Pauwels RA.
Time course of bronchodilating effect of inhaled formoterol, a potent and long acting sympathomimetic. Thorax 1992;47:30-33.

4. Faulds D, Hollingshead LM, Goa KL.
Formoterol. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. Drugs 1991;42:115-137.

5. Grønnerød TA, von Berg A, Schwabe G, Soliman S.
Formoterol via Turbuhaler® gave better protection than terbutaline against repeated exercise challenge for up to 12 hours in children and adolescents. Respiratory Medicine 2000: 94 (7):661-667

6. Ind P, Börszörmenyi Nagy G, Pietinalho A, Shiner R, Villasante C, Brander R, Larsson P.
Formoterol 4.5 mcg, used as needed via Turbuhaler® was as safe and well tolerated as terbutaline 0.5 mg. Eur Resp J 1999;ERS-99 (P1086).

7. Löfdahl C-G, Svedmyr N.
Formoterol fumarate, a new β_2-adrenoceptor agonist. Acute studies of selectivity and duration of effect after inhaled and oral administration. Allergy 1989;44:264-271.

8. Mak JCW, Grandordy B, Barnes PJ.
High affinity [^{3}H]formoterol binding sites in lung: characterization and autoradiographic mapping. Eur J Pharmacol 1994;269:35-41.

9. National Institute of Health, Global Strategy for Asthma Management and Prevention, NHLBI/WHO Workshop Report, March 1993, Publication #95-3659, January 1995.

10. Nelson HS, Weiss, ST, Bleeckeer ER, Yancey SW, Dorinsky PM, and SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol. CHEST, 2006;129:15-26

11. Pauwels RA, Löfdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A.
Effect of inhaled formoterol and budesonide on asthma exacerbations. N Engl J Med, 1997;337:1405-11.

12. Politiek MJ, Boorsma M, Aalbers R.
Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. Eur Respir J 1999;13:988-992.

13. Ramsdale EH, Otis J, Kline PA, Gontovnick LS, Hargreave FE, O'Byrne PM.
Prolonged protection against methacholine-induced bronchoconstriction by the inhaled β_2-agonist formoterol. Am Rev Respir Dis 1991;143:998-1001.

14. Rott Z, Böcskei C, Poczi M, Juhász, Larsson P, Rosenborg J.
On the relative therapeutic index between formoterol Turbuhaler® and salbutamol pressurized metered dose (pMDI) inhaler in asthmatic patients. Eur Respir J 1998;12(Suppl 28):324s.

15. Sasaki H, Kamimura H, Enjoji Y, Shiobara Y.
Absorption and distribution of formoterol fumarate in rats. Oyo Yakuri 1983;25(6):981-991.

16. Scheurs AJM et al.
A dose-response study with formoterol Turbuhaler as maintenance therapy in asthmatic patients. ERJ 1996;9:1678-1683.

17. Seberová E and A Andersson.
Oxis® (formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by pMDI. Respiratory Medicine 2000, 94, 607-611.

18. Tattersfield A, Löfdahl CG, Postma DS, Ekström T, Eivindson A, Schreurs A, Rasidakis A, Karlsson K, Larsson P.
On demand treatment: Comparison of formoterol and terbutaline in moderate asthma. Am J Respir Crit Care Med 1999;159 (No. 3 Pt 2):A636.

19. The 1999 Canadian Asthma Consensus Report.
Canadian Medical Association Journal, November 30, 1999; 161 (11 Suppl).

20. Tötterman KJ, Huhti L, Sutinen E, Backman R, Pietinalho A, Falck M, Larsson P, Selroos O.
Tolerability to high doses of formoterol and terbutaline via Turbuhaler® for 3 days in stable asthmatic patients. Eur Respir J 1998;12:573-579.

21. Trofast J, Österberg K, Källström B-L, Waldeck B.
Steric aspects of agonism and antagonism at β-adrenoceptors: Synthesis of and

pharmacological experiments with the enantiomers of formoterol and their diastereomers. Chirality 1991;3:443-450.

22. van der Molen T, et al.
Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. Thorax 1996;52:535-539.

23. Vilsvik J, Ankerst J, Palmqvist M, Persson G, Schaanning J, Schwabe G, Johansson Å.
Protection against exercise-induced bronchoconstriction during regular treatment with formoterol Turbuhaler® b.i.d. in adult asthmatics. Eur Resp J 1999;ERS-99 (P1085).

24. Wallin A, Sandström T, Rosenhall L, Melander B.
Time course and duration of bronchodilatation with formoterol dry powder in patients with stable asthma. Thorax 1993;48:611-614. Correction Thorax 1993;48:1188. Letters to the Editor Thorax 1994;49:95.

25. Wegener T, Hedenström H, Melander B.
Rapid onset of action of inhaled formoterol in asthmatic patients. Chest 1992;102:535-538.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr OXEZE® TURBUHALER®

formoterol fumarate dihydrate dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when OXEZE TURBUHALER was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about OXEZE TURBUHALER. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What the medication is used for:
OXEZE TURBUHALER is used to help breathing problems in patients with asthma and its related conditions **only as an add-on therapy to an inhaled corticosteroid**. Your doctor has prescribed OXEZE TURBUHALER because you or your child's asthma is not well controlled with current asthma medications (e.g. inhaled glucocorticosteroids along with an as needed short-acting bronchodilator medication). An inhaled glucocorticosteroid must always be used if you or your child is using OXEZE TURBUHALER.

The efficacy and safety of OXEZE TURBUHALER in children younger than 6 years has not been established.

Note to Parents: It is important that you watch your child(ren) to make sure that they take both OXEZE TURBUHALER **and** an inhaled corticosteroid at the same time. If you cannot ensure that your child(ren) is taking **both** medications at the same time, then talk to your doctor. A combination product may be required.

What it does:
When taken regularly with an inhaled corticosteroid, twice daily maintenance treatment with OXEZE TURBUHALER gives 24 hour relief or prevention of symptoms such as shortness of breath in patients with asthma and its related conditions.

Formoterol is a fast-acting bronchodilator with a long duration of action. It widens the airways enabling you to breathe more easily. You usually notice an effect from OXEZE TURBUHALER within 1-3 minutes.

When it should not be used:
OXEZE TURBUHALER should not be used to provide relief for a sudden attack of breathlessness.

Remember:
- Do not take OXEZE TURBUHALER without an inhaled corticosteroid. If you are being treated for asthma, you should always be given both OXEZE TURBUHALER and an inhaled corticosteroid to use together. The inhaled corticosteroid decreases the inflammation in your lungs while OXEZE TURBUHALER opens the airways. A third drug, a relief medication, should be used for any sudden attacks of breathlessness (asthma attacks).
- Do not use OXEZE TURBUHALER if you are allergic to formoterol or inhaled lactose (which may contain milk protein residue).
- Do not use OXEZE TURBUHALER if you have a heart problem called tachyarrhythmia (fast and/or irregular heart beat).

What the medicinal ingredient is:
Formoterol fumarate dihydrate.

What the nonmedicinal ingredients are:
Lactose monohydrate (which may contain milk protein residue).

What dosage forms it comes in:
Dry powder for oral inhalation: 6 mcg and 12 mcg/dose. Each inhaler contains 60 doses.

WARNINGS AND PRECAUTIONS

Serious Warnings for Asthma Patients
OXEZE TURBUHALER may increase the risk of asthma-related death. It may increase the risk of asthma-related hospitalizations in pediatric and adolescent patients. Therefore,
- OXEZE TURBUHALER must **only** be used as an **add-on** therapy when your inhaled corticosteroid does not adequately control your asthma symptoms.
- OXEZE TURBUHALER must always be used together with an inhaled corticosteroid.
- The dose of OXEZE TURBUHALER may be reduced or discontinued by your doctor when your asthma is assessed as adequately under control (step-down therapy).

For any concerns regarding the use of OXEZE TURBUHALER, consult your doctor.

BEFORE you use OXEZE TURBUHALER talk to your doctor or pharmacist:
- about all health problems you have now or have had in the past, especially if you have a heart disorder, diabetes, or a disturbed thyroid function (thyrotoxicosis);

- if you have ever had a bad, unusual or allergic reaction to formoterol or lactose or to other medicines for breathing problems;
- if you are pregnant, plan to become pregnant or are breast feeding.

When to call your doctor:
If you are using more of your fast-acting bronchodilator medication or if you feel that it is less effective TELL YOUR DOCTOR RIGHT AWAY. Your doctor may adjust your treatment.

If your symptoms are waking you up at night, TELL YOUR DOCTOR RIGHT AWAY. Your doctor may adjust your treatment.

If you have taken all your medication as instructed by your doctor and your symptoms are not relieved or you notice a sudden worsening of your shortness of breath, YOU MAY NEED EMERGENCY TREATMENT.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Drugs that may interact with OXEZE TURBUHALER include:
- beta-blockers (some heart medicines or eye drops).

PROPER USE OF THIS MEDICATION

The dosage of OXEZE TURBUHALER is individual. Follow your doctor's instructions carefully. They may differ from the information contained in this leaflet.

Asthma:

For the maintenance treatment of asthma, OXEZE TURBUHALER should be taken at the same time with an anti-inflammatory medication, such as a corticosteroid to reduce the inflammation in your lungs due to your asthma. Your anti-inflammatory medication and OXEZE TURBUHALER are designed to work together to best treat your condition. You must continue to regularly take the anti-inflammatory medications your doctor has given you. Even if you feel better, DO NOT STOP or reduce your doses of either the anti-inflammatory medication or OXEZE TURBUHALER without first checking with your doctor.

Usual Adult Dose: 6 mcg or 12 mcg twice a day, taken 12 hours apart. Some adults may need to take 24 mcg, twice a day.
Maximum daily dose: 48 mcg a day.

Usual Child (6-16 years old) Dose: 6 or 12 mcg twice a day, taken 12 hours apart.
Maximum daily dose: 24 mcg a day.

Note to Parents: It is important that you watch your child(ren) to make sure that they take both OXEZE TURBUHALER **and** an inhaled corticosteroid at the same time. If you cannot ensure that your child(ren) is taking **both** medications at the same time, then talk to your doctor. A combination product may be required.

For the prevention of exercise-induced asthma:

Usual Adult and Child (6 years of age and older) Dose: 6 or 12 mcg before you exercise.
Maximum Adult Dose: 48 mcg in a 24 hour period.
Maximum Child and Adolescent Dose: 24 mcg in a 24 hour period.

Do NOT take more than the dose prescribed by your doctor.

You should see your doctor if:
- your usual dose does not provide relief;
- the effects of one dose last less than 12 hours;
- you use more than 48 mcg of OXEZE TURBUHALER for 3 days in a row.

These may be signs that your asthma is getting worse.

Missed Dose:
If you miss a dose and you remember within 6 hours, you should take it as soon as possible. You should then go back to your regular schedule. However, if it has been more than 6 hours when you remember, do not take the missed dose. Just take the next dose on time.

Never take a double dose of OXEZE TURBUHALER to make up for missed doses. If you are still unsure, check with your doctor or pharmacist to see what you should do.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

There is no clinical experience on the management of overdose. The most common signs and symptoms of an overdose are:
- trembling;
- headache;
- rapid heartbeat.

HOW TO USE YOUR OXEZE TURBUHALER INHALER
Before you start using OXEZE TURBUHALER for the first time it is important that you read the instructions below and follow them carefully.

TURBUHALER is a multidose inhaler from which very small amounts of powder are administered. When you breathe in through TURBUHALER the powder is delivered to the lungs. It is therefore important that you **inhale as deeply and strongly** as you can through the mouthpiece.

Before you use a **NEW** inhaler for the first time you must prepare the inhaler for use. Follow the steps under "**A. How to prepare a NEW inhaler for use:**".

For regular use of your inhaler follow the steps under "**B. How to take a dose:**".

A. How to prepare a NEW inhaler for use:

You only need to prepare your **NEW** inhaler for use **once**. You do not need to repeat these steps even if your inhaler is not used regularly.

STEP 1 Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **greenish-blue grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the greenish-blue grip as far as it will go in the opposite direction (Figure 2).
- At some point when you are turning the grip, **you will hear a "click".** This is part of the preparation process.

Figure 2

STEP 3 **Repeat STEP 2** one more time. Then follow the steps under "**B. How to take a dose:**", **starting at STEP 2**.

B. How to take a dose:

To properly take a dose, follow these 4 steps:

STEP 1 Unscrew and lift off the cover (Figure 1). You will hear a rattling sound when you unscrew the cover. This is normal.

Figure 1

STEP 2 Hold the inhaler upright. Do not hold the inhaler by the mouthpiece.

- Turn the **greenish-blue grip** as far as it will go in one direction (clockwise or counter-clockwise, it does not matter which way you turn it first).
- Then turn the greenish-blue grip as far as it will go in the opposite direction (Figure 2).

Figure 2

A dose has now been loaded.

- At some point when you are turning the grip, **you will hear a "click".** This is part of the loading process.

NOTE: If you accidentally **drop**, **shake** or **breathe out** into OXEZE TURBUHALER after the dose has been loaded, you will lose your dose. If this happens, repeat STEP 2 to load a new dose.

STEP 3 **Breathe out**, with your mouth away from the mouthpiece (Figure 3). Then, place the mouthpiece gently between your teeth.

Figure 3

STEP 4 Now close your lips over the mouthpiece. Do not bite or chew the mouthpiece.

- **Inhale as deeply and strongly** as you can (Figure 4).
- You may not feel or taste the medication when inhaling. This is common.
- Before you exhale, remember to remove the inhaler from your mouth.

Figure 4

Repeat STEPS 2-4 if more than one dose has been prescribed. When you have taken the prescribed number of doses, **replace the cover and screw it back on**.

Note: Do not try to take off the mouthpiece or to twist it unnecessarily. The mouthpiece can be rotated but it is fixed to the inhaler and must not be taken off. Do not use the TURBUHALER if it has been damaged.

I cannot remember how many times I turned the greenish-blue grip. What should I do?

The TURBUHALER is designed to load only one dose at a time. If you can't remember how many times you have turned the greenish-blue grip, you can start the process again. Follow the steps below. You will not end up loading two doses.

If you are using a **NEW** inhaler for the first time, start at the beginning of STEP 2 under the section "**A. How to prepare a NEW inhaler for use:**".

For regular use of your inhaler, start at the beginning of STEP 2 under the section "**B. How to take a dose:**".

How do I know my dose has been loaded?

By turning the greenish-blue grip all the way in BOTH directions, you will properly load a dose of your medication. At some point when you are turning the grip you will hear a "click". This is part of the loading process. If you are not sure you heard the "click", repeat from the beginning of STEP 2 under the section "**B. How to take a dose:**". This will not result in two doses being loaded. The TURBUHALER is designed to load only one dose at a time.

How do I clean my inhaler?

Clean the outside of the mouthpiece once a week with a **dry** tissue. **Never** use water or any other fluid. If fluid enters the inhaler it may not work properly.

How do I know when to start a new inhaler?

OXEZE TURBUHALER has a dose indicator. The dose indicator tells you around how many doses are left in the inhaler. The dose indicator moves slowly each time you load a dose. Every 20th dose is marked with a number and every 10th dose is marked with a dash (Figure 5). For the last 10 doses, the background of the indicator is red. When the "0" on the red background has reached the middle of the window, you should throw out your inhaler and start a new inhaler. The sound you hear if you shake the inhaler is made by a drying agent, not medication. OXEZE TURBUHALER cannot be refilled with the drug and should be thrown away.

Figure 5

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Usually you do not feel any side effects when you use OXEZE TURBUHALER. However, like any medication, OXEZE TURBUHALER may cause side effects in some people.

Side effects are:
- headache;
- trembling;
- dizziness;
- nausea;
- muscle cramps;
- skin rash;
- changes in the salt balance in the blood (low potassium levels);
- high blood sugar levels;
- rapid heartbeat;
- sleep disturbances;
- variations in blood pressure;
- hypertension;
- behaviour disturbances;
- agitation;
- restlessness;
- nervousness.

Side effects that do occur are usually mild and disappear by themselves within one or two weeks of treatment, however, be sure to tell your doctor if any of the side effects bother you or if they continue.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only if severe	In all cases	
Unknown	Chest pain		X	
	Sudden shortness of breath and wheezing shortly after inhalation of OXEZE			X
	Irregular heartbeat		X	
	Bronchospasm (shortness of breath, chest tightness)			X
	Allergic Reactions Lumpy skin rash or hives anywhere on the body, or itching			X

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only if severe	In all cases	
	Allergic Reactions Sudden wheeziness and chest pain or tightness; or swelling of eyelids, face or lips			X

***If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.**

This is not a complete list of side effects. For any unexpected effects while taking OXEZE TURBUHALER, contact your doctor or pharmacist.

HOW TO STORE IT

Remember to **keep OXEZE TURBUHALER out of the reach and sight of children.**

Always replace the cover after using OXEZE TURBUHALER. Store the inhaler at room temperature (15-30°C)**.**

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Call toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

The Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.astrazeneca.ca,
or by contacting the sponsor, AstraZeneca Canada Inc. at: 1-800-668-6000.

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