National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

ZOTREX SYRUP

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zotrex Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of solution contains 2mg salbutamol as salbutamol sulfate.

Excipient with known effect:
Sodium benzoate, benzyl alcohol, propylene glycol
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.

A clear, colourless to pale straw coloured liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zotrex Syrup is indicated for the treatment or prevention of bronchospasm. It provides short acting bronchodilation in reversible airways obstruction due to asthma and chronic obstructive pulmonary disease (COPD) such as chronic bronchitis and emphysema.

Zotrex Syrup is indicated in adults, adolescents and children aged 2 to 12 years.

4.2 Posology and method of administration

Posology

Adults (over 18 years)
10 to 20 ml of Syrup (4 to 8 mg salbutamol) three or four times daily.

Paediatric Population
Children aged 2 to 6 years: 2.5 to 5 ml of Syrup (1 to 2 mg salbutamol) three or four times daily. Children aged 6 to 12 years: 5 ml of Syrup (2 mg salbutamol) three or four times daily.
Children aged over 12 years: 5 to 10 ml of Syrup (2 to 4 mg salbutamol) three or four times daily.

Special patient groups
In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 5ml of Syrup(2 milligram salbutamol) three or four times per day.

Method of Administration

Salbutamol has a duration of action of 4 to 6 hours in most patients.

Increasing use of beta-2 agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be

increased on medical advice.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Bronchodilators should not be the only or main treatment in patients with persistent asthma. In patients with persistent asthma unresponsive to salbutamol, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with salbutamol may signal a need for urgent medical advice or treatment.

Increasing use of short-acting inhaled beta-2 agonists to control symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted

Patients should be warned that if either the usual relief is diminished or the usual duration of action reduced, they should not increase the dose or its frequency of administration, but should seek medical advice.

Salbutamol causes peripheral vasodilation which may result in reflex tachycardia and increased cardiac output. Caution should be used in patients with angina, severe tachycardia or thyrotoxicosis.

Potentially serious hypokalaemia may result from beta-2 agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

In common with other beta-adrenoceptor agonists, Ventolin can induce reversible metabolic changes, for example increased blood sugar levels. The diabetic patient may be unable to compensate for this and the development of ketacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml dose, that is to say essentially 'sodium-free'. Zotrex Syrup is sugar free.

This medicine contains 10 mg sodium benzoate in each 5 ml dose which is equivalent to 2 mg/ml.

This medicine contains 1.9 mg of propylene glycol in each 5 ml dose.

Zotrex Syrup contains trace amounts of benzyl alcohol in each dosage unit. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called 'gasping syndrome') in young children. Benzyl alcohol may cause allergic reactions. Patients with liver or kidney disease and pregnant or breastfeeding patients should be advised that large amounts of benzyl alcohol can build up in the body and may cause metabolic acidosis.

4.5 Interaction with other medicinal products and other forms of interactions

Salbutamol and non-selective β-blocking drugs, such as propranolol, should not usually be prescribed together.

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs), however the effects of salbutamol may be altered by guanethidine, reserpine, methyldopa and tricyclic antidepressants.

Caution should be exercised in it's use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

4.6 Fertility, pregnancy and lactation

Pregnancy
Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; this indicates its well-established use in the management of premature labour. However, as with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the foetus at very high dose levels.

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

Breast-feeding
As salbutamol is probably secreted in breast milk its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk.

It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Fertility
There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common reactions were generally determined from clinical trial data. Rare and very rare reactions were generally determined from spontaneous data.

Immune system disorders	
Very rare:	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.
Metabolism and nutrition disorders	
Rare:	Hypokalaemia
	Potentially serious hypokalaemia may result from beta-2 agonist therapy
Nervous system disorders	
Very common:	Tremor.
Common:	Headache.
Very rare:	Hyperactivity.
Cardiac disorders	
Common:	Tachycardia, palpitations.

Rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Unknown: Myocardial ischaemia* (see section 4.4). * reported spontaneously in post-marketing data therefore frequency regarded as unknown **Vascular disorders:**	
Rare:	Peripheral vasodilatation.
Musculoskeletal and connective tissue disorders	
Common:	Muscle cramps.
Very rare:	Feeling of muscle tension.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see sections 4.4 and 4.8).

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored.

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

Treatment
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-2-adrenoceptor agonist
ATC code: R03A C02

Salbutamol is a selective beta-2 adrenoceptor agonist. At therapeutic doses it acts on the beta-2 adrenoceptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation in reversible airways obstruction. It is suitable for the management and prevention of attack in asthma.

5.2 Pharmacokinetic properties

Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally and partly by metabolism to the inactive 4'-O-sulfate (phenolic sulfate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After oral administration, salbutamol is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine.

The bioavailability of orally administered salbutamol is about 50%.

5.3 Preclinical safety data

In common with other potent selective beta-2 receptor agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of foetuses were found to have cleft palate, at 2.5mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50mg/kg/day, 78 times the maximum human oral dose.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of salbutamol up to 50 mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid monohydrate
Hypromellose
Sodium benzoate (E211)
Saccharin sodium
Orange flavour IFF 17.42.8187 (contains benzyl alcohol & propylene glycol)
Sodium chloride
Purified water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Dilution of Zotrex Syrup with syrup BP or sorbitol solution is not recommended as this may result in precipitation of the cellulose thickening agent.

6.3 Shelf life

3 years
Diluted solution: 4 weeks. Discard any unused diluted solution.

6.4 Special precautions for storage

Store below 30°C.
Store in the original container to protect from light.
Keep out of reach of children

6.5 Nature and contents of container
100ml amber glass bottle

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Dispose as directed by local health authorities

7 APPLICANT/MANUFACTURER

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