Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salamol CFC-Free Inhaler 100 micrograms pressurised inhalation, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains salbutamol sulfate equivalent to 100 micrograms salbutamol.

Excipients with known effect:
Each metered dose contains 3.93 mg ethanol anhydrous.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

Pressurised container fitted with a metering valve.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Salamol is indicated for the treatment or prevention of bronchospasm. It provides short acting (four hours) bronchodilation in reversible airways obstruction due to asthma and chronic obstructive pulmonary disease (COPD) such as chronic bronchitis and emphysema. For patients with asthma salbutamol may be used to relieve symptoms when they occur and to prevent them prior to a known trigger.

Salamol is indicated in adults, adolescents and children. For babies and children under 4 years of age, see sections 4.2 and 5.1.

4.2 Posology and method of administration

Salamol is administered by the inhaled route only, to be breathed in through the mouth.

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 corticosteroid therapy should be considered.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult, a spacer may be used with Salamol.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

Patients' inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

Adults and adolescents (children 12 years and over)

Relief of acute bronchospasm:
100 or 200 micrograms.

On demand use of Salamol should not exceed four times daily. Reliance on such supplementary use or a sudden increase in dose indicates deteriorating asthma (see section 4.4).

Prevention of recognised allergen or exercise-induced bronchospasm:
200 micrograms before challenge or exertion.

Chronic therapy:
Up to 200 micrograms four times daily.

Elderly:
There is no need to adjust the dose in the elderly.

Paediatric Population

Babies and young children using Salamol may benefit from the use of a paediatric spacer device with a face mask.

Relief of acute bronchospasm:
The usual dosage for children under the age of 12 years: 100 micrograms. The dose may be increased to 200 micrograms if required.

Children aged 12 years and over: 100 or 200 micrograms.

On demand use of Salamol should not exceed four times daily. Reliance on such supplementary use or a sudden increase in dose indicates deteriorating asthma (see section 4.4*).*

Prevention of recognised allergen or exercise-induced bronchospasm:
The usual dosage for children under the age of 12 years: 100 micrograms before challenge or exertion. The dose may be increased to 200 micrograms if required.

Children aged 12 years and over: 200 micrograms before challenge or exertion.

Chronic therapy:
The usual dosage for children under the age of 12 years: Up to 200 micrograms four times daily.

Children aged 12 years and over: Up to 200 micrograms four times daily.

Testing your inhaler
Before using for the first time remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release two puffs into the air to make sure that it works. If it has not been used for 5 days or more, shake it well and release two puffs into the air to make sure that it works.

Using your inhaler

1. Remove the mouthpiece cover by gently squeezing the sides of the cover.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it.
6. Just after starting to breathe in through your mouth press down on the top of the inhaler to release salbutamol while still breathing in steadily and deeply.
7. While holding your breath, take the inhaler from your mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable.
8. If you are to take further puffs keep the inhaler upright and wait about half a minute before repeating stages 3 to 7.
9. Replace the mouthpiece cover by firmly pushing and snapping the cap into position.

IMPORTANT
Do not rush Stages 5, 6 and 7. It is important that you start to breathe in as slowly as possible just before operating your inhaler.

Practise in front of a mirror for the first few times. If you see 'mist' coming from the top of the inhaler or the sides of your mouth you should start again from stage 2.
If your doctor has been given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Cleaning
Your inhaler should be cleaned at least once a week.

1. Remove the metal canister from the plastic casing of the inhaler and remove the mouthpiece cover.
2. Rinse the actuator thoroughly under warm running water.
3. Dry the actuator THOROUGHLY inside and out.
4. Replace the metal canister and mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

4.3 Contraindications

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

Although intravenous salbutamol is used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, inhaled salbutamol presentations are not appropriate for managing premature labour. Salbutamol preparations should not be used for threatened abortion.

4.4 Special warnings and precautions for use

Salamol is particularly valuable as rescue medication in mild, moderate or severe asthma, provided that reliance on it does not delay the introduction and use of regular inhaled corticosteroid therapy.

Salbutamol should be administered cautiously to patients with thyrotoxicosis, coronary insufficiency, cardiac arrhythmias, hypertension or diabetes mellitus.

The management of asthma should normally follow a stepwise programme, and the patient response should be monitored clinically and by lung function tests. Severe asthma requires regular medical assessment as death may occur.

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 bronchodilators, in particular $ß_2$-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.

In the event of a previously effective dose of inhaled salbutamol failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

Patients requiring long term management with salbutamol should be kept under regular surveillance.

A responsible adult should supervise the use of the inhaler in children.

As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

In common with other beta-adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported.

Potentially serious hypokalaemia may result from $ß_2$-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.

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. The specific salbutamol presentation should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

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 medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per metered dose.

4.5 Interaction with other medicinal products and other forms of interactions

Propranolol and other non-cardioselective ß-adrenoreceptor blocking agents antagonise the effects of salbutamol, and 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.

Digoxin: risk of increased cardiovascular effects.

Caution should be exercised during the concurrent use of anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

Hypokalaemia occurring with $ß_2$-agonist therapy may be exacerbated by treatment with diuretics.

Because of the content of ethanol, there is a theoretical potential for interaction in patients taking disulfiram or metronidazole.

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.

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.

Salbutamol inhalation is contraindicated in treatment of premature labour.

Breastfeeding
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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare and very rare events 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 $ß_2$-agonist therapy.

Nervous system disorders
Common: Tremor, headache
Very rare: Hyperactivity

Cardiac disorders
Common: Tachycardia
Uncommon: Palpitations
Very 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

Respiratory, thoracic and mediastinal disorders
Very rare: Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator. Salamol should be discontinued immediately, the patient assessed, and if necessary alternative therapy instituted.

Gastrointestinal disorders
Uncommon: Mouth and throat irritation

Musculoskeletal and connective tissue disorders
Uncommon: Muscle cramps

Paediatric population
There are reports about stimulating effects on the central nervous system after inhalation of salbutamol which manifest themselves in hyperexcitability, hyperactive behaviour, sleeping disturbances and hallucinations. These observations were predominantly made in children up to 12 years of age.

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 section 4.4 and section 4.8).

Overdosage may result in skeletal muscle tremor, tachycardia and headache.

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.

The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective $ß_2$-adrenoreceptor agonists, ATC Code: R03AC02

Salbutamol is a selective $ß_2$-adrenoceptor agonist. At therapeutic doses it acts on the $ß_2$-adrenoceptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

Special Patient Populations
Children < 4 years of age:
Paediatric clinical studies conducted at the recommended dose (SBO20001, SBO30001, SBO30002), in patients <4 years with bronchospasm associated with reversible obstructive airways disease, show that salbutamol has a safety profile comparable to that in children ≥ 4 years, adolescents and adults.

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 administration by the inhaled route between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation but is not metabolised by the lung.

On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate.

The swallowed portion of an inhaled dose 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.

5.3 Preclinical safety data

Salamol CFC-Free Inhaler:
Toxicological studies in rats and dogs with salbutamol formulated in propellant HFA-134a have shown a comparative safety profile to the current CFC-containing products. Few adverse effects were noted at high doses, which were consistent with the known effects of salbutamol inhalation.

Propellant HFA-134a:
Toxicological effects of propellant HFA-134a consisted of narcosis and a relatively weak cardiac sensitising potential at very high exposure concentrations only. Safety margins of 2200, 1314 and 381 for mouse, rat and dog with respect to humans have been observed.

HFA-134a has been shown to be non-toxic at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

Salbutamol:
In common with other potent selective $ß_2$-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 2.5 mg/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.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post-partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofetal development, litter size, birth weight or growth rate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol Anhydrous
Norflurane (Hydrofluoroalkane – 134a (HFA-134a))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

As with most inhaled medication in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold.

The canister should not be broken, punctured or burnt, even when apparently empty. The canister contains a pressurized liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

6.5 Nature and contents of container

The can is of 14 ml brimful capacity, manufactured from deep drawn aluminium with either a debossed or plain base, and is supplied with a metering valve, of 25 microlitres nominal dosing capacity. Each inhaler supplies a minimum of 200 metered doses.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
T/A IVAX Pharmaceuticals Ireland
Unit 301
IDA Industrial Park
Cork Road, Waterford
Ireland

8 MARKETING AUTHORISATION NUMBER

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