Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salbutamol CFC Free 100 micrograms per metered dose Pressurised Inhalation, Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains salbutamol sulfate equivalent to 100 micrograms.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pressurised inhalation, suspension.

Pressurised aluminium container closed with a metering valve containing a white or almost white suspension (see also section 6.5).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Salbutamol CFC Free is indicated in adults, adolescents and children aged 4 to 11 years. For babies and children under 4 years of age, see sections 4.2 and 5.1.

Salbutamol CFC Free is indicated in the management of bronchial asthma, for the relief of wheezing and shortness of breath used on an as required basis. Salbutamol CFC Free may be used as necessary to relieve attacks of acute dyspnoea and may be used to prevent recognised allergen or exercise induced bronchospasm.

Salbutamol CFC Free may also be used in the treatment of reversible airways obstruction associated with chronic bronchitis and emphysema.

4.2 Posology and 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.

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.

Posology

Adults: For the relief of wheezing, shortness of breath and attacks of acute dyspnoea in patients with asthma, or reversible airways obstruction associated with chronic bronchitis and emphysema, one (100 micrograms) or two inhalations (200 micrograms) may be administered as a single dose.

For prophylaxis of recognised allergen or exercise-induced asthma, two inhalations (200 micrograms) before challenge or exertion is recommended.

For chronic therapy up to two inhalations (200 micrograms) is recommended up to four times daily.

Older people: No special dosage recommendations are made for older patients.

Paediatric population
Children (aged 4 to 11 years): For the relief of wheezing, shortness of breath and attacks of acute dyspnoea in children under 12 years of age with asthma, one inhalation (100 micrograms) which may be taken as a single minimum (starting) dose, increasing to two inhalations (200 micrograms) if necessary may be administered as a single dose.

For prophylaxis of recognised allergen or exercise-induced asthma, one inhalation (100 micrograms) is recommended before challenge or exertion. The dose may be increased to two inhalations (200 micrograms) if necessary.

For chronic therapy, the recommended dosage for children under the age of 12 years: up to two inhalations (200 micrograms) 4 times daily.

Children (aged 12 years and over): Dose as per adult population.

All patients

The maximum recommended dose in any 24 hours should not exceed 8 inhalations (equivalent to 800 micrograms). With repetitive dosing, inhalations should not usually be repeated more often than every 4 hours. Reliance on such frequent supplementary use, or a sudden increase in dose indicates poor control of or worsening asthma (see also section 4.4).

The safety and efficacy of Salbutamol CFC Free inhaler in children under 4 years of age has not yet been established. No data are available.

Other pharmaceutical forms may be more appropriate for administration to children under 4 years of age.

Method of administration (see also PIL for pictograms)

For inhalation use.

1. Remove the dust cap from the mouthpiece of the actuator (plastic case) by holding it between the thumb and forefinger and squeezing gently whilst pulling them apart. Check that there are no objects in the mouthpiece and that it is clean.
2. Hold the inhaler upright with your thumb on the base and your first finger on the top of the can, and shake well.
3. Breathe out slowly thorough your mouth as far as is comfortable and then immediately place the mouthpiece of the actuator fully into your mouth between your teeth and close your lips lightly around it, but don’t bite it.
4. Breathe in slowly and deeply and as you start to do so press the metal canister down firmly with your first finger to spray the aerosol and release the medicine. This action delivers a measured amount of salbutamol.
5. Relax the pressure on the metal canister. Continue to breathe in steadily and deeply.
6. Remove the mouth piece of the actuator from your mouth while holding your breath for about 10 seconds, or as long as comfortable, then breathe out slowly.
7. If your doctor instructs you to take a further puff, wait for about one minute, keeping the inhaler upright and then repeat steps 2 to 6.
8. Replace the dust cap on the mouthpiece by snapping it into place to protect the mouthpiece from dirt and dust.

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.

Test Firing
Test the inhaler if it is new or has not been used for more than one week by shaking it well and firing two puffs into the air to check that it works.

If your Salbutamol CFC Free gets very cold, remove the metal canister from the actuator and warm it by rolling between your hands. DO NOT USE ANY OTHER SOURCE OF HEAT TO WARM IT UP.

Cleaning
Clean the inhaler once a week. To clean it:

1. Remove the metal canister by gripping it firmly and pulling it out of the actuator. Then remove the dust cap from the actuator.
2. Clean the mouthpiece and dust cap in warm water. You can also add a mild detergent or baby bottle cleaning solution to the water; your pharmacist can advise you about this. If you use a cleaning solution rinse the actuator and dust cap in running water. DO NOT put the metal canister into water.
3. Dry the actuator and dust cap thoroughly inside and out. Avoid excessive direct heat. Replace the dust cap and metal canister by reversing step 1.

Caution
The canister is pressurised – do not puncture or expose the canister to excessive heat even when empty.

4.3 Contraindications

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

Salbutamol is contraindicated for use in the management of premature labour and threatened abortion.

4.4 Special warnings and precautions for use

Salbutamol 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.

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

The management of asthma should normally follow a stepwise programme, and 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 severe or unstable asthma. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled steroid treatment (*e.g.* > 1 mg/day beclometasone dipropionate) or oral corticosteroid therapy. With this primary background corticosteroid treatment, salbutamol provides essential rescue medication for a severe asthmatic in treating acute exacerbations. Failure to respond promptly or fully to such rescue medication, signals a need for urgent medical advice and treatment.

Increasing use of short-acting inhaled beta 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. As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. 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 or their asthma seems to be worsening, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

Potentially serious hypokalaemia has been reported in patients taking beta-2-agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in patients with acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics, long-term laxatives and by hypoxia. Extra care should therefore be taken if beta-2-agonists are used in these groups of patients and serum potassium levels should be monitored.

Unwanted stimulation of cardiac adrenergic receptors can occur in patients taking beta-2-agonist therapy.

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 beta agonists. 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.

The patient should be advised to seek medical advice if the treatment ceases to be effective and/or their asthma seems to be worsening, and not to increase the dose without medical advice.

Administer cautiously to patients with angina, severe tachycardia or thyrotoxicosis.

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

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and non-selective beta-blockers, such as propranolol, should not usually be prescribed together.

Hypokalaemia occurring with beta-2-agonist therapy may be exacerbated by treatment with xanthines, steroids, diuretics and long-term laxatives.

Caution should be exercised in the use of salbutamol with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

The effects of salbutamol may be altered by guanethidine, reserpine, methyldopa, tricyclic antidepressants and, monoamine oxidase inhibitors (MAOIs).

4.6 Fertility, pregnancy and lactation

Pregnancy
Salbutamol CFC Free should not be used in pregnancy unless the expected benefit to the mother is thought to outweigh any possible risk to the foetus or neonate.

In mice and rabbits large doses of salbutamol have been shown to be teratogenic (see section 5.3).

During post 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
Salbutamol CFC Free should not be used in nursing mothers unless the expected benefit to the mother is thought to outweigh any potential risk to the neonate. Salbutamol is probably secreted in breast milk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

4.7 Effects on ability to drive and use machines

Salbutamol CFC Free has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Reported adverse reactions are listed in the following table per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data). Rare and very rare events were generally determined from spontaneous data.

Immune system disorders	
Rare	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse
Metabolism and nutrition disorders	
Rare	Hypokalaemia Potentially serious hypokalaemia has been reported in patients taking beta-2-agonist therapy
Nervous system disorders	
Uncommon Very rare	Tremor, headache Hyperactivity
Cardiac disorders	
Common Uncommon Very rare Not known	Tachycardia Palpitations Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardias and extrasystoles Myocardial ischaemia has been reported spontaneously in post-marketing data (see section 4.4).
Vascular disorders	
Rare	Peripheral vasodilation
Respiratory, thoracic and mediastinal disorders	
Very rare	Paradoxical bronchospasm As with other inhalation therapy, paradoxical bronchospasm may occur immediately after dosing. In this instance, Gerivent CFC Free should be discontinued immediately and alternative therapy instituted if necessary.
Gastrointestinal disorders	
Uncommon	Mouth and throat irritation
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle cramps

Paediatric population

Psychiatric disorders	
Rare	Hyperactivity

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
Earlsfort Terrace
IRL - Dublin 2.
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

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.

Management

Consideration should be given to discontinuation of treatment.

Asthmatic patients: Monitor biochemical abnormalities, particularly hypokalaemia which should be treated with potassium replacement where necessary. Beta-adrenoceptor antagonists, even beta-1-selective antagonists, are potentially life-threatening and should be avoided.

Non-asthmatic patients: Monitor and correct biochemical abnormalities, particularly hypokalaemia. A non-selective beta-adrenoceptor antagonist (*e.g.* nadolol, propranolol) will competitively reverse both hypokalaemia and tachycardia (beta-1-selective drugs will be largely ineffective).

Beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics, inhalants, selective beta-2-adrenoreceptor agonists, ATC code: R03AC02

Mechanism of action
Salbutamol is a sympathomimetic agent which has a selective action on beta-2-adrenergic receptors in bronchial smooth muscle with little or no action on the beta-1-adrenoceptors of the heart. With its fast onset of action, onset (within 5 minutes) in reversible airways obstruction due to asthma, chronic bronchitis and emphysema, it is particularly suitable for the management and prevention of attacks in mild asthma and for the treatment of acute exacerbations in moderate and severe asthma.

Salbutamol should be used to relieve symptoms when they occur and to prevent them in those circumstances recognised by the patient to precipitate an asthmatic attack (*e.g.* before exercise or unavoidable allergen exposure).

Clinical efficacy and safety
Clinical experience over many years indicates continuing symptomatic benefit on airways obstruction on a long term basis.

Paediatric population
Children < 4 years of age:
Paediatric clinical studies conducted at the recommended dose 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

Absorption
Salbutamol is readily absorbed from the gastrointestinal tract, but the systemic absorption of the inhaled drug substance is low. Between 10-20% 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.

The action of inhaled salbutamol depends on direct stimulation of receptors in the lung. Onset of action is usually within 10 minutes of inhalation and lasts 4-6 hours in most patients.

Distribution
Salbutamol is bound to plasma proteins to the extent of 10%.

Biotransformation and elimination
Salbutamol, on reaching the systemic circulation or as the swallowed portion of an inhaled dose and absorbed from the gastrointestinal tract is subject to first-pass metabolism in the liver; primarily in the urine as unchanged drug and an inactive phenolic sulfate conjugate. It does not appear to be metabolised in the lung and therefore its fate following inhalation therapy depends on the delivery method used, which determines the proportion of salbutamol inhaled relative to the proportion inadvertently swallowed. It has been suggested that the slightly extended half-life following inhalation may reflect slow removal of active drug from the lungs. The majority of dose is excreted within 72 hours.

5.3 Preclinical safety data

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 50 mg/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 50 mg/kg/day, 78 times the maximum human oral dose. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Oleic acid
Norflurane (HFA 134a)
Ethanol, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

The canister contains a pressurised liquid.
Do not expose to temperatures higher than 50°C.
Do not store above 25°C. Protect from frost and direct sunlight.
Do not pierce the canister.

6.5 Nature and contents of container

A pressurised metered dose inhaler consisting of:
- A blue "L" shaped plastic actuator with a removable dust cap at one end

and

- An aluminium container, with a silver ferrule valve.

Each complete unit contains 200 metered doses.

6.6 Special precautions for disposal and other handling

Patients should be advised fully on the technique for using their inhaler by referencing the full list of instructions provided in the Patient Information Leaflet. Instructions for use and cleaning are presented in section 4.2.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd.
T/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/091/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th February 2010

Date of last renewal: 26th February 2015

10 DATE OF REVISION OF THE TEXT

November 2015