SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Easyhaler Salbutamol Sulfate 200 micrograms per actuation inhalation powder

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metered dose delivery 200 mcg of Salbutamol per actuation as Salbutamol Sulfate Ph.Eur.

Excipient with known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

White or almost white odourless powder intended for respiratory use by oral inhalation

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of asthma attacks and exacerbations of asthma in adults and children aged 4 years and over. Prevention of exercise-induced bronchospasm or before exposure to a known unavoidable allergen challenge. Symptomatic treatment of broncho-asthma and other conditions associated with reversible airways obstruction.

Salbutamol provides a short-acting bronchodilation with fast onset of action in reversible airways obstruction due to asthma.

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

Salbutamol is valuable as a 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.

Easyhaler Salbutamol Sulfate is indicated in adults, adolescents and children aged 4 to 11 years.

4.2 Posology and method of administration

Posology

Adults and Older people:
For the relief of acute bronchospasm and for managing intermittent episodes of asthma one inhalation (200 micrograms) may be administered as a single starting dose, this may be increased to two inhalations (400 micrograms).

To prevent exercise-induced bronchospasm or allergen bronchospasm one inhalations (200 micrograms) should be taken before challenge, this dose (200 micrograms) may be repeated if necessary.

Paediatric Population:
Relief of acute bronchospasm
Children aged 4 to 11 years 200 micrograms as required.
Children aged 12 years and over: Dose as per adult population.

Prevention of allergen or exercise-induced bronchospasm
Children aged 4 to 11 years 200 micrograms before challenge or exertion.
Children aged 12 years and over: Dose as per adult population.

Chronic therapy
Children aged 4 to 11 years 200 micrograms four times a day.
On-demand use of Easyhaler Salbutamol Sulfate should not exceed four times daily. Reliance on such frequent supplementary use, or a sudden increase in dose, indicates poorly controlled or deteriorating asthma (see section 4.4).
Children aged 12 years and over: Dose as per adult population.

On demand use of Easyhaler Salbutamol Sulfate should not exceed four inhalations (800 micrograms) in any 24 hour period.

For optimum results in most patients Easyhaler Salbutamol Sulfate inhaler should be used regularly during asthmatic attacks. The bronchodilator effect of each administration of inhaled salbutamol lasts for four hours, except in patients whose asthma is becoming worse. Such patients should be warned not to increase their usage of salbutamol, but should seek medical advice in case treatment with an inhaled and/or systemic glucocorticosteroid is indicated.

Method of administration

For oral inhalation only.

This preparation is particularly useful for patients unable to use metered dose inhalers properly and for patients in whom the use of an inhalation aerosol causes irritation of airways. Inhaled salbutamol should be used only on as-needed basis at the lowest dose and frequency required.

Precautions to be taken before handling or administering the medicinal product

Instructions for use:

The protective cover of the inhaler should be opened and the dust cap removed immediately prior to use.

The inhaler should be shaken vigorously up and down 3-5 times. Whilst holding the inhaler in an upright position, between the finger and thumb, press once until a click is heard. Let inhaler click back again whilst continuing to hold in an upright position.

Inhalation should take place from either a sitting or standing position. The patient should breathe out normally and place the mouthpiece between their teeth whilst using their lips to form a seal around the mouthpiece. Patients are instructed to perform a rapid and forced inhalation through the Easyhaler device. After holding their breath for at least 5 seconds the patient can resume normal breathing. Patients should not to exhale into the device.

The mouthpiece of the inhaler should be cleaned once a week using a dry cloth or tissue.

Patients should be instructed in the proper use of their inhaler (see patient information leaflet) and children should always have adult supervision when using the device. Illustrated instructions for use accompany each package.

4.3 Contraindications

Hypersensitivity to salbutamol or to the excipient listed in section 6.1 (lactose monohydrate, which contains small amounts of milk proteins).

Salbutamol inhalation is contraindicated in treatment of threatened abortion or premature labour.

4.4 Special warnings and precautions for use

Patients who are prescribed regular anti-inflammatory therapy (e.g., inhaled corticosteroids) should be advised to continue taking their anti-inflammatory medication even when symptoms decrease, and they do not require Salbutamol.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma.

Severe asthma requires regular medical assessment including lung function testing as the patients are at risk of severe attacks and even death. Physicians should consider using oral corticosteroid therapy or the maximum use of inhaled corticosteroids. Increasing use of bronchodilators, particularly short-acting inhaled $ß_2$-agonists to relieve symptoms indicates deteriorating asthma control (especially if the peak expiratory flow rate value falls and/or becomes irregular), and patients should be warned to seek medical advice as soon as possible.

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.

Patients who take more than twice a week “as needed” salbutamol, not counting prophylactic use prior to exercise, should be re-evaluated (i.e., daytime symptoms, night-time awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of salbutamol.

In the event of a previous effective dose of inhaled salbutamol failing to give relief for at least three hours or if they need more inhalations than usual, the patient should

be advised to seek medical advice as soon as possible. In this situation patients should be reassessed and consideration given to an increase in their anti-inflammatory therapy, (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids). A regular anti-inflammatory controller medication taken on a daily basis is required as soon as the patient needs inhaled Beta2-agonists more than twice a week. Severe episodes of asthma must be treated in the normal way.

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

Salbutamol should be administered with caution in patients with thyrotoxicosis, cardiac insufficiency, hypokalaemia, myocardial ischaemia, tachyarrhythmia and hypertrophic obstructive cardiomyopathy.

Potentially serious hypokalaemia may result from ß$_2$-agonist therapy, mainly from parenteral and nebulised therapy. 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(see section 4.5).

Rarely inhalation therapy may cause bronchospasm after dosing. In this event, treatment with Salbutamol must be immediately discontinued and, if need be, replaced with another therapy.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences 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.

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. Concurrent administration of glucocorticoids can exaggerate this effect.

One dose contains less than 10 mg lactose, which probably does not cause symptoms in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

If additional adrenergic drugs are administered to patients using Salbutamol Easyhaler they should be used with caution to avoid deleterious cardiovascular effects.

Concomitant administration of salbutamol and non-selective ß-blocking drugs such as Propranolol is not recommended.

Patients treated with monoamine oxidase inhibitors or tricyclic antidepressants should be followed clinically in the beginning of salbutamol treatment, because the action of salbutamol on the vascular system may be potentiated.

The simultaneous administration of xanthines, corticosteroids or potassium excreting diuretics may increase hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnant women has not been established. No controlled clinical trials with salbutamol have been conducted in pregnant women. Rare reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received. Some of the mothers were taking multiple medications during their pregnancies. 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.

Breast-feeding

As salbutamol is excreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother outweighs any potential risk to the neonate.

Fertility

There is no information on the effects of salbutamol on human fertility.

4.7 Effects on ability to drive and use machines

Salbutamol Easyhaler has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects caused by normally used inhaled doses of Salbutamol are mild, typical for sympathomimetic agents, and they usually disappear with continued treatment.

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), very rare (<1/10,000) and not known (cannot be estimated from the available data).

	Common	**Uncommon**	**Rare**	**Very Rare**
Immune System disorders		hypersensitivity reactions (angioedema, urticaria, hypotension		

		and collapse)		
Metabolism and nutrition disorders			hypokalaemia	
Nervous system disorders		Headache	hyperactivity, restlessness, dizziness	Sleep disturbances
Cardiac disorders	palpitations			myocardial ischaemia Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Vascular disorders	peripheral vasodilatation, and as a result small increase in heart rate			
Respiratory, thoracic and mediastinal disorders			bronchospasm (see section 4.4), cough, irritation of mouth and throat which may be prevented by rinsing the mouth after inhalation.	
Musculoskeletal and connective tissue and bone disorders:	tremor		muscle cramps,	

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Excess repeat use of inhalations may produce adverse effects such as tachycardia, CNS stimulation, tremor, hypokalaemia and hyperglycaemia.

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.

Treatment consists of discontinuation of salbutamol together with appropriate symptomatic therapy. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but beta-blocking drugs should be used with caution in patients with a history of bronchospasm. Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored. If hypokalaemia occurs potassium replacement via the oral route should be given. In patients with severe hypokalaemia intravenous replacement may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta2-adrenoreceptor agonists. ATC code: R03AC02.

Salbutamol is a selective ß $_2$-adrenergic receptor agonist. The pharmacological effects of salbutamol are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5',-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. Salbutamol also stimulates mucous secretion and mucociliary transport in the respiratory tract. Bronchial effects of inhaled salbutamol can be detected after a few minutes and duration of action is normally 4-6 hours.

Like other ß $_2$-adrenoceptor agonists salbutamol also has cardiovascular effects in some patients as measured by changes in pulse rate, blood pressure, symptoms and ECG changes. These effects can especially be detected after oral and intravenous administration of salbutamol. Furthermore oral and intravenous salbutamol causes reduction in uterine tonicity which has been associated with pain relief in pregnancy. In addition, salbutamol has some metabolic effects. Especially intravenous and nebulised salbutamol decreases serum potassium concentrations although the effect is generally mild and transient. Salbutamol has also lipolytic effects and it has been shown to cause increases in blood glucose and insulin probably by stimulating glycogenolysis and having a stimulatory effect on ß $_2$-receptors in pancreas cells.

5.2 Pharmacokinetic properties

Absorption

Orally administered salbutamol is well absorbed with peak plasma concentrations occurring 1 to 4 hours after administration.

Distribution

The major proportion of inhaled Salbutamol is swallowed. The fraction that is distributed to the lung (approx. 10-25%) is rapidly seen in the circulation as free unmetabolised drug. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism.

Elimination

The plasma concentrations of inhaled Salbutamol are, however, lower than those produced by usual oral doses. Salbutamol and its metabolites are rapidly excreted in the urine and faeces with about 80% of the dose being recovered in urine within 24 hours. The elimination half-life of Salbutamol is 2.7 - 5.5 hours after oral and inhaled administration.

5.3 Preclinical safety data

The short term toxicity has been tested in different animal species - the mouse, the rat and the dog - at doses extending to several thousand fold higher than the intended human therapeutic dose - maximally in the region of 15 µg/kg daily. The lethal doses via the intravenous route in the rodents range from 50mg/kg, via the peroral route to around 2000 mg/kg and even higher. Thus the agent exhibits low acute systemic toxicity.
Local toxicity on the airway has not been exclusively studied, but the historical evidence based on long clinical use suggests good airway tolerance.

Reported findings in repeated dose studies such as tachycardia, increases in heart weight and hypertrophy of muscle fibres are common to all potent selective beta2-agonists and are an expression of excessive beta-stimulant action. The safety margin for these effects is not known.

The subacute toxic effects on the cardiac muscle are seen at doses ranging from 0.2 to 3mg/kg. This is a manifestation of the pharmacodynamics of salbutamol at grossly elevated doses.

The doses administered in subchronic toxicity studies have been in the milligram ranges per kilogram - 0.15 to 50 - via the oral route or by inhalation. The species have been the rat (p.o. administration), and the dog (p.o. and inhalation). The toxic signs and symptoms exhibited were, as noted in the paragraph above, related to the mode of action on the adrenergic receptor.

The chronic toxicity, again, is manifested as exaggerated pharmacodynamic effects in animals.

Animal data on reproductive toxicity is quite limited. Sympathomimetics, including salbutamol, are widely used in clinical medicine in patients of fertile age. In spite of

this fact, no adverse reproductive effects attributable to salbutamol are reported in the literature.

Embryotoxicity in animal studies seems to be related only to the mouse. In this species the union of the flat bones of the lower part of the skull seem to be involved. The specific mechanism of this has not been fully elucidated.

Foetal toxicity at high single or elevated chronic doses are related to energy metabolism from glycogen. Catecholamines liberate energy in the form of glucose from glycogen stored in liver and muscle. This action is mediated by glycogen synthase and phosphorylase of these tissues. Elevated foetal insulin and glucose levels suggest a higher sensitivity of the foetal pancreas to this stimulation of ß -adrenergic receptors.

The classic airways of mutagenic potential by which this agent has been tested have exhibited no increase in the incidence of mutations.

The potential of increase in the number of neoplasms shows a species and even a strain specificity, as did the effect on the delay in union flat jaw bones. Ovarian leiomyomas, benign tumours of smooth muscle, occur with a significantly higher frequency in the rat, particularly of the Spraque-Dawley strain. The other rodent species do not appear to be affected, suggesting a difference in the susceptibility of the uterine muscle of Spraque-Dawley to ß -adrenergic stimulation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (contains milk protein)

6.2 Incompatibilities

None

6.3 Shelf life

Unopened: 3 years

After first opening of foil pouch: 6 months

6.4 Special precautions for storage

Store in a dry place at a temperature not exceeding 25°C.

6.5 Nature and contents of container

The multidose powder inhaler (Easyhaler) consists of seven plastic parts and a stainless steel spring.

The plastic materials of the inhaler are polyester, LDPE, polycarbonate, acetal, styrene butadiene, polypropylene.

The inhaler is wrapped in laminate foil and packed in a cardboard box.

The starting package contains an inhaler and a protective cover. The maintenance pack contains the dry powder inhaler only.

Pack size: 200 actuations.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PL 27925/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of latest renewal: 1 June 2003

10 DATE OF REVISION OF THE TEXT

12/11/2025