1. NAME OF THE MEDICINAL PRODUCT

Buventol Easyhaler™ 100 mcg/ dose Inhalation Powder
Buventol Easyhaler™ 200 mcg/ dose Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Buventol Easyhaler™ is an inhalation powder packed into a multiple dose powder inhaler from which the patient can accurately deliver the individual drug doses. It is for oral inhalation.

Buventol Easyhaler™ 100 mcg/ dose Inhalation Powder: The product contains salbutamol sulphate equivalent to 100 mcg of salbutamol per metered dose. The dose, which the patient gets through the mouthpiece of the device is 90 mcg of salbutamol.

Buventol Easyhaler™ 200 mcg/ dose Inhalation Powder: The product contains salbutamol sulphate equivalent to 200 mcg of salbutamol per metered dose. The dose, which the patient gets through the mouthpiece of the device is 180 mcg of salbutamol.

The Buventol Easyhaler™ multiple dose powder inhaler contains 200 doses of finely powdered salbutamol sulphate mixed in a small quantity of lactose. The amount of drug received by the patient (90 or 180 mcg/dose) corresponds to that from salbutamol inhalation aerosol. The dose to be inhaled is released from the container by pressing the device between the thumb and forefinger. This is followed by inhalation through the device. As a result, salbutamol particles are transferred to their target, the lungs. Use of the Buventol Easyhaler™ does not require coordination of actuation of the dose and inhalation.

3. PHARMACEUTICAL FORMS

Inhalation powder.
White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Symptomatic treatment of acute asthma attack.
- Prevention of exercise-induced bronchospasm.
- Symptomatic treatment of bronchial asthma and other conditions, such as bronchitis and emphysema, associated with reversible airways obstruction.

4.2 Posology and method of administration

The preparation is intended for oral inhalation only. This preparation is particularly useful for patients who are unable to use metered dose inhaler properly and for patients to whom the use of inhalation aerosol causes irritation of airways. The lowest effective doses of inhaled salbutamol are recommended and instead of regular use it is recommended to use inhaled salbutamol when needed.

Adults: For the relief of acute asthma or before exercise 100 - 400 mcg. The recommended dose for maintenance treatment or prophylactic therapy is 100 - 400 mcg two to four times a day. Maximum dose is 2.4 mg / day.

Children: In the treatment of episodic asthma or before exercise 100 - 200 mcg. The recommended dose for maintenance or prophylactic treatment is 100 - 200 mcg two to four times daily. Maximum dose is 1.2 mg / day.

Instruction for use/ handling:
Patients have to be instructed to perform a strong and deep inhalation through the Easyhaler™ device. Patients have to be instructed not to exhale into the device. Illustrated user's instructions for use accompany each package.

4.3 Contraindications
Known hypersensitivity to salbutamol or to milk proteins (the excipient lactose contains milk proteins)

Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 Special warnings and precautions for use
Rapidly increasing use of short-acting inhaled $beta_2$-agonists to relieve symptoms, indicates deterioration of asthma control (especially if peak expiratory flow rate value falls and/or becomes irregular). Patients should therefore be advised that in these cases the doctor's advice should be obtained as soon as possible, and therapeutic management should then be reassessed.

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.

Salbutamol should be given with caution in patients suffering from thyreotoxicosis, cardiac insufficiency, hypokalaemia, myocardial ischemia, tachyarrhythmia and hypertrophic obstructive cardiomyopathy.

Potassium levels should be monitored in severe asthma as hypokalaemia potentially caused by salbutamol may be potentiated by concomitant treatment and by hypoxia (see section 4.5.)

Rarely inhalation therapy may cause bronchospasm after dosing. In this event, treatment with Salbutamol Easyhaler™ 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 Interactions with other medicinal products and other forms of interactions
If additional adrenergic drugs are administered to patients using Salbutamol Easyhaler™ they should be used with caution to avoid deleterious cardiovascular effects. Patients treated with monoamino 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. Beta-blockers,

such as propranolol, inhibit the effect of salbutamol like that of any other $beta_2$-agonists.

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

4.6 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 salbutamol during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Lactation: As salbutamol is excreted in breast milk its use in nursing mothers requires careful consideration. As it is not known whether salbutamol has harmful effects on the neonate, its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh 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
The effect of Salbutamol Easyhaler™ on the ability to drive and use machines has not been directly studied. From the well-known pharmacological actions of salbutamol and decades of clinical experience such effects are, however, regarded as unlikely.

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.

The most common adverse effects of salbutamol include peripheral vasodilatation and as a result small increase in heart rate, palpitations and tremor. Other adverse effects of salbutamol include headache, hypersensitivity reactions (angioedema, urticaria, hypotension and collapse), bronchospasm (see section 4.4), cough, irritation of mouth and throat which may be prevented by rinsing the mouth after inhalation, hypokalaemia, muscle cramps, hyperactivity, restlessness, dizziness and cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles, myocardial ischaemia (see section 4.4).

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 Easyhaler™ together with appropriate symptomatic therapy. If hypokalaemia occurs potassium replacement via 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.

The pharmacologic effects of salbutamol are at least in part attributable to stimulation through

betaadrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes 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. Bronchial effects of inhaled salbutamol can be detected after few minutes and duration of action is normally 4-6 hours.

Like other beta$_2$-adrenoceptor agonists also salbutamol 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. In addition, salbutamol has some metabolic effects. Especially intravenous and nebulized salbutamol decreases serum potassium concentrations although the effect is generally mild and transient.

5.2 Pharmacokinetic properties
After administration of salbutamol by the inhaled route between 10 and 25% of the dose reaches the lung. 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. The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism. Both unchanged drug and conjugate are excreted primarily in the urine. The elimination half-life of salbutamol is 2.7 to 5.5 hours after oral and inhaled administration.

5.3 Preclinical safety data
Acute toxicity of salbutamol is low in the mouse, rat and dog. LD50 values in these species have exceeded several thousand fold the intended human therapeutic doses. Reported findings in repeated dose studies such as tachycardia, increases in heart weights and hypertrophy of muscle fibres are common to all potent selective beta2-agonists and are an expression of excessive beta-stimulant action. Cleft palate has been reported in mice but not in rats or rabbits after subcutaneous administration. Salbutamol is not mutagenic. Mesovarian leiomyomas, benign tumours of smooth muscle, occur particularly in Sprague-Dawley rats, but not in other species.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate (contains milk protein).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years when stored in laminate pouch, 6 months after opening of the pouch.
Buventol Easyhaler™ should not be used after these dates.

6.4 Special precautions for storage and other handling
Store in a dry place, not exceeding 25 °C.
Keep out of reach of children.

6.5 Nature and contents of container
Buventol Easyhaler™ 100 mcg/ dose Inhalation Powder:
A User Package containing 1 unit of Buventol Easyhaler™ 100 mcg/dose inhalation powder in the inhaler device, and instruction for use.

Buventol Easyhaler™ 200 mcg/ dose Inhalation Powder:
A User Package containing 1 unit of Buventol Easyhaler™ 200 mcg/dose inhalation powder in the inhaler device, and instruction for use.

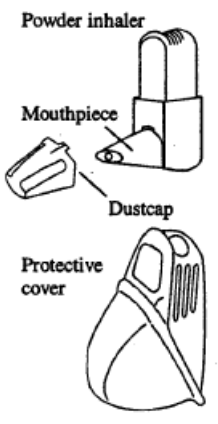
INSTRUCTIONS FOR USE
Buventol Easyhaler®
Salbutamol inhalation powder

Read the following instructions before using Buventol Easyhaler™ inhalation powder. Follow the instructions carefully.

With Buventol Easyhaler™ multidose powder inhaler you can inhale salbutamol to your lungs without needing to inhale any propellants.

The powder inhaler contains 200 doses of salbutamol, which is a bronchodilating drug substance used in the prophylaxis and treatment of asthma attacks.

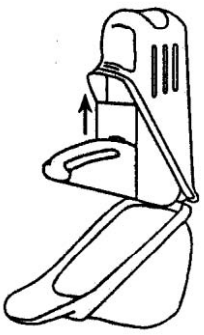
Figure 1.



A. PREPARING THE POWDER INHALER FOR FIRST USE

1. Remove the powder inhaler from the laminate pouch.
If you *do not use the protective cover* move on to point B.

Figure 2.

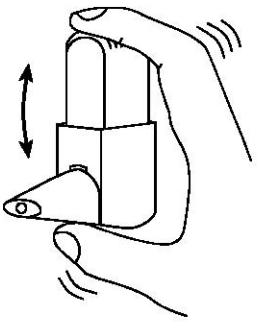


If you use the protective cover:
2. Open the protective cover.
3. Insert the powder inhaler into the protective cover (Figure 2). The dustcap on the mouthpiece (Figure 1) prevents accidental actuation of the inhaler when inserting it into the protective cover.
4. If you are not using the device immediately, close the protective cover. Store the inhaler in the protective cover when not in use.

B. **DELIVERING THE MEDICATION**

Figure 3.
1. Remove the dustcap (Figure 1).

Figure 3.

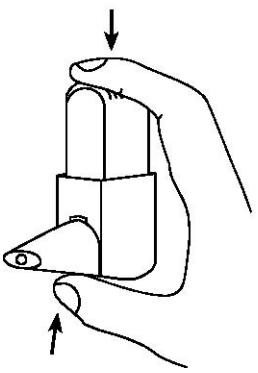


2. Shake the device prior to each dose (Figure 3).
After shaking**, hold the device** in the upright position.

3. **Release the dose.**

Figure 4.
Press the device only once between your thumb and forefinger until you hear a click (Figure 4).
Let the device return to the original position. Keep holding the device in the upright position.

Figure 4.

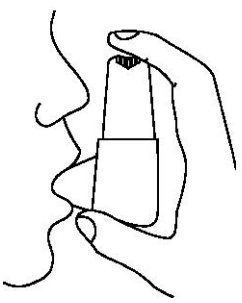


Note! If you think that you have released more than one dose, remove the doses from the mouthpiece by tapping it against the palm of your hand or, for example, a table, as shown in Figure 6. After this, repeat from point 2 (Shake the device...).

Figure 5.
4. **Inhale the drug dose** according to the following instructions:

- *First* breath out normally.
- *Then* place the mouthpiece in your teeth and close

Figure 5.

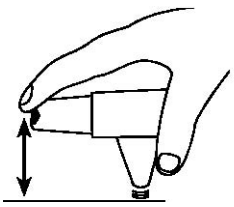


your lips tightly around the mouthpiece.

- **Take a strong and deep breath through your mouth** (Figure 5).
- Remove the inhaler from your mouth and hold your breath for 5 to 10 seconds.
- When you feel a sweet taste in your mouth, which is not felt by everybody, you can be sure that you have received the dose.

If you have been prescribed more than one dose, repeat points 2, 3 and 4 (Shake the device..., Release the dose, Inhale the drug...).

Figure 6.



5**. Put the dustcap back on the mouthpiece.**

CLEANING

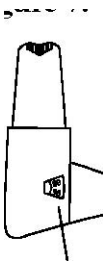
The mouthpiece can be cleaned with a dry cloth. **Never use water!**

STORAGE

Store the powder inhaler in a dry place, not exceeding 25°C.

Figure 7.

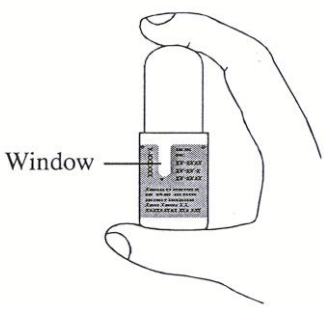
WHEN SHOULD THE DEVICE BE RENEWED?



The expiry date is printed on the package. Do not use the product if it is expired. Once the inhaler is removed from its laminate pouch, it must be used within six months. Do not use the product if it has been outside the pouch longer than six months.

Figure 8.

The inhaler has a dose counter which indicates the number of remaining doses (Figure 7). The counter turns after every five actuations. When the counter turns red there are 20 doses left. A clear window on the back of the inhaler allows viewing of the powder (Figure 8). The device must be replaced when the dose counter indicates zero.



IMPORTANT

Release the dose from the device only when you are going to inhale the medication. If you have accidentally released the dose, remove it from the mouthpiece by tapping it against the palm of your hand or, for example, a table (Figure 6).

Inhalation powder should not be exposed to humidity. If the powder becomes damp, it is not suitable for use and should be disposed of.

Never exhale into the powder inhaler, because the humidity of exhalation damages the product.

Manufactured by: Orion Corporation, Espoo, Finland
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