SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL PRODUCTS

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Buto-Asma Inhaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each application contains 100 micrograms of salbutamol (equivalent to 120 micrograms of salbutamol sulphate).

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution

4 CLINICAL PARTICULARS

4.1.*Therapeutic indications*

- Symptomatic treatment of bronchospasm in bronchial asthma and in other processes associated with reversible obstruction of the airways.

- Prophylaxis of bronchospasm induced by physical exercise or before exposure to a known and unavoidable allergen stimulus.

4.2.*Posology and method of administration*

Posology

Adults:

In order to relieve acute bronchospasm and to treat intermittent asthma episodes, one inhalation may be administered as a single dose. This can be increased to two inhalations if necessary. If the response is inadequate, doses greater than two inhalations may be used. The maximum recommended dose is two inhalations, three or four times per day.

In order to prevent exercise-induced bronchospasm, one or two inhalations should be administered 15 minutes before exercising.

One or two inhalations can be administered before expected contact with allergens.

Use in adults over 65/80 years of age:

The same recommendations as for adults.

Paediatric population:

The recommended dose for relieving acute bronchospasm in the treatment of episodic asthma, or for preventing exercise-induced asthma, is a single inhalation. If the response is inadequate, doses greater than one inhalation may be used.

On-demand use should not exceed four inhalations per day. The bronchodilator effect of each application of inhaled salbutamol lasts at least four hours, except for patients whose asthma is worsening. These patients should be warned not to increase their use of the inhaler, but to see their doctor in case it is necessary to increase the dose of inhaled glucocorticoid treatment or systemic glucocorticoid administration.

The need for additional use or a sudden increase in the dose indicate a worsening of the asthma.

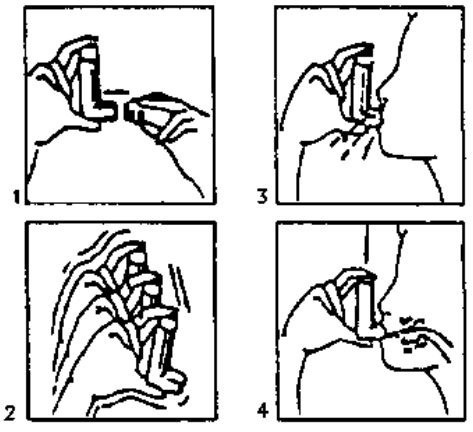
As excessively high-dose-related adverse effects may occur, the dose or frequency of administration should only be increased by doctor's prescription.

4.3.*Method of administration*

Method of administration
For administration by inhalation only:

A. Remove the cap (fig. 1). If it is a new inhaler or it has not been used for several days, shake the inhaler (fig. 2) and press the canister down to check that the inhaler is working correctly. If the inhaler is used regularly, skip to the following instructions:

B Shake the inhaler (fig. 2).
C Exhale as much air as possible from your lungs.
D. Place the inhaler in your mouth as shown in the picture (fig. 3).
E. Inhale as deeply as possible.
Press down on the device as you inhale, as shown in the arrows in the picture (fig. 4).



F. Remove the inhaler from your mouth and try to keep the air in your lungs for a few seconds.
G. You should wash the inhaler's canister and mouthpiece regularly. To do this, remove the canister from the inhaler and rinse with plenty of water.
H. Store with the cap on to protect it from dust and dirt.

Patients who find it difficult to coordinate breathing in with using the pressurised suspension for inhalation should use a spacer.

The container is pressurised. It should not be pierced, broken or burned, even when it appears to be empty.

4.4.*Contraindications*

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

4.5.*Special warnings and precautions for use*

Treatment of asthma should normally follow a staggered regimen, and patient response should be monitored clinically and by lung function tests.

Bronchodilators should not be the only or main treatment for patients with persistent mild, moderate, severe or unstable asthma. Severe asthma requires regular medical check-ups, including lung function tests, as patients are at risk of suffering severe attacks and even death. In these cases, the doctor should consider prescribing the maximum recommended dose of inhaled corticosteroids or oral administration of corticosteroids.

An increasing use of inhaled short-acting bronchodilators, particularly beta-2 agonists, to relieve symptoms indicates deterioration of asthma control. The doctor should warn the patient that if they notice that the short-acting bronchodilator treatment becomes less effective or they need to take more inhalations than usual, they should consult their doctor immediately. In such cases, the patient's therapy should be reassessed, along with the need to increase anti-inflammatory treatment (e.g. higher doses of inhaled corticosteroids or a cycle of oral corticosteroids).

A sudden and progressive deterioration in asthma control may be potentially life-threatening and starting or increasing corticosteroid therapy should be considered. Daily peak flow monitoring can be performed in patients considered at-risk.

If a previously effective inhaled dose of salbutamol does not provide relief for at least three hours, the patient should be advised to consult the doctor so that additional measures can be taken.

The patient's inhalation technique should be checked.

Salbutamol should be administered with caution to patients with thyrotoxicosis, hypertension, known aneurysms, reduced glucose tolerance, manifest diabetes, pheochromocytoma and concomitant use of cardiac glycosides.

Cardiovascular effects may occur with any sympathomimetic agent, including this medicinal product. There is some evidence of myocardial ischaemia associated with beta agonists obtained from post-marketing data and scientific articles. Patients with severe underlying heart disease (e.g. Cardiac ischaemia, arrhythmia or severe heart failure) who are being treated with salbutamol, should be advised to see their doctor if they develop chest pain or other symptoms of worsening heart disease. Symptoms such as dyspnoea and chest pain should be carefully assessed, as they may have both respiratory and cardiac origin.

Beta-2 agonist therapy can lead to potentially severe hypokalaemia, mainly after the administration of parenteral and nebulised presentations. Particular caution is advised in acute severe asthma, as this effect may be enhanced by concomitant treatment with xanthine derivatives, steroids and diuretics, and by hypoxia. Monitoring of serum potassium levels is recommended in such situations.

Salbutamol and non-selective beta blockers such as propranolol should not normally be prescribed for concomitant administration.

Use in athletes

Athletes should be warned that this medicine contains salbutamol, which may give a positive result in a doping test.

4.6.*Paediatric population*

The recommended dose for relieving acute bronchospasm in the treatment of episodic asthma, or for preventing exercise-induced asthma, is a single inhalation. If the response is inadequate, doses greater than one inhalation may be used.

On-demand use should not exceed four inhalations per day. The bronchodilator effect of each application of inhaled salbutamol lasts at least four hours, except for patients whose asthma is worsening. These patients should be warned not to increase their use of the inhaler, but to see their doctor in case it is necessary to increase the dose of inhaled glucocorticoid treatment or systemic glucocorticoid administration.

The need for additional use or a sudden increase in the dose indicate a worsening of the asthma.

As excessively high-dose-related adverse effects may occur, the dose or frequency of administration should only be increased by doctor's prescription.

4.7. *Interaction with other medicinal products and others forms of interaction*

Salbutamol should not be administered together with other sympathomimetic bronchodilator inhalers. If adrenergic drugs must also be administered by any route, caution should be exercised to prevent harmful cardiovascular effects.

Salbutamol should be administered with caution in patients treated with monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants, as the action of salbutamol on the vascular system may be enhanced.

Salbutamol and non-selective beta blockers such as propranolol should not normally be administered together. Caution is also recommended in patients taking cardiac glycosides.

Potentially serious hypokalaemia has occurred as a result of systemic treatment with beta-2 agonists. Particular caution is advised in acute severe asthma, as this effect may be enhanced by concomitant treatment with xanthine derivatives, corticosteroids and diuretics, and by hypoxia.

As salbutamol may reduce serum potassium, caution should be exercised in patients who are taking drugs that reduce serum potassium, as the effects may be additive.

Patients should be informed that, whenever possible, they should discontinue treatment with salbutamol at least 6 hours before an expected anaesthetic with halogenated anaesthetics.

4.8. *Additional information on special populations*

Not applicable.

4.9. *Fertility, pregnancy and lactation*

Pregnancy

Administration should only be considered during pregnancy and breast-feeding if the expected benefit to the mother outweighs the possible risk to the foetus.

Over the course of extensive worldwide marketing experience, cases of congenital abnormalities, including cleft palate and limb defects, have been reported in the children of patients treated with salbutamol. Some mothers received multiple medications during pregnancy and no relationship with salbutamol can be established. However, animal studies revealed some harmful effects on the foetus at very high doses.

Breast-feeding

If salbutamol needs to be administered to a breast-feeding mother, , it is recommended to replace breast-feeding. Salbutamol can be excreted in breast milk and it is not known whether it is harmful to the newborn.

4.10. *Effects on ability to drive and use machines*

The ability to drive and use machines may be affected in patients who have individual adverse reactions, especially at high doses, particularly at the start of treatment or if administered together with alcohol.

Possible side effects of salbutamol, such as transient muscle cramps and tremor, may necessitate caution when using machines.

4.11. *Undesirable effects*

The undesirable effects are dose-dependent and are due to the mechanism of action of the beta-2 agonists.

On very rare occasions, hypersensitivity reactions have been reported, including angioedema and urticaria, bronchospasm, hypotension and fainting.

Circulatory and lymphatic system disorders: potentially serious hypokalaemia may occur as a result of systemic treatment with beta-2 agonists. Special care should be taken in patients with hypokalaemia who take beta-2 agonists due to the increased risk of tachycardia and arrhythmias. Hypokalaemia may be enhanced by concomitant treatment with corticosteroids, diuretics and xanthines.

Psychiatric disorders: nervousness, feeling of tension. Just as with other beta-2 agonists, there have been rare reports of hyperactivity in children.

Nervous system disorders: mild tremor, headache, dizziness.

Cardiovascular disorders: tachycardia, angioedema, hypotension. Cases of cardiac arrhythmias related to the beta-2 agonists have been reported (including atrial fibrillation, supraventricular tachycardia and extrasystole), normally in susceptible patients.
Unknown: myocardial ischaemia* (see section 4.4)

Respiratory, thoracic and mediastinal disorders: as with any other inhaled therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after administration. This should be treated immediately with an alternative presentation or with a different fast-acting inhaled bronchodilator. Administration of salbutamol in the form of a pressurised suspension for inhalation should be discontinued immediately, the patient should be re-assessed and, if necessary, alternative therapy should be started.

Gastrointestinal disorders: nausea.

Skin and subcutaneous disorders: urticaria.

Musculoskeletal system, connective tissue and bone disorders: there have been rare reports of temporary muscle cramps.

General disorders and administration site conditions: cases of oral and pharyngeal irritation may occur.

*Spontaneous notifications from post-marketing data, so the frequency is classified as not known.

4.12. Overdose

Overdose should be treated symptomatically.
The preferred antidote for salbutamol overdose is a cardioselective beta blocker. However, beta-blockers should be used with caution in patients with a history of bronchospasm.

Hypokalaemia may occur after an overdose with salbutamol. Serum potassium levels should be monitored and any deficiency replaced with oral potassium, except in patients with severe hypokalaemia where intravenous administration may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Bronchodilators and other inhaled antiasthmatic drugs (R03A1).
ATC code: R03A C02.

Mechanism of action
Salbutamol is an adrenergic bronchodilator that stimulates beta-2-adrenergic receptors in the lungs to relax bronchial smooth muscle, thereby relieving bronchospasm, increasing vital capacity, reducing residual volume and reducing airway resistance. This ensures rapid bronchodilation within a few minutes which persists for 4 to 6 hours.

Pharmacodynamic effects
It is believed that this action is a result of the increased production of 3',5'-cyclic adenosine monophosphate (AMP—3',5'cyclic or AMP-c) produced by the activation of the adenylate cyclase enzyme, an enzyme that catalyses the conversion of adenosine triphosphate (ATP) to AMP-c. The increase in AMP-c concentrations, in addition to relaxing bronchial smooth muscle, inhibits the release of mediators of immediate hypersensitivity of cells, especially mastocytes.

Clinical efficacy and safety

Salbutamol has a greater effect on the respiratory tract than isoproterenol, but causes fewer cardiovascular effects due to its greater affinity for beta-2-adrenergic receptors. Its duration of action is longer than that of isoproterenol, as it is not a substrate for catecholamine cell uptake processes or catechol-O-methyltransferase.

Salbutamol also causes vasodilation, which causes a reflex chronotropic effect and general metabolic effects, including hypokalaemia.

5.2. Pharmacokinetic properties

Absorption
After inhalation of salbutamol, only around 10% or less of the drug is deposited in the airways, and the rest is swallowed. Salbutamol is well absorbed in the gastrointestinal tract.

Distribution
Due to its gradual absorption from the bronchi, systemic salbutamol levels are low after inhalation of recommended doses. Peak plasma concentrations of salbutamol occur after 2 to 4 hours.

Metabolism or Biotransformation

The pre-systemic metabolism of salbutamol is significant and occurs primarily in the gastrointestinal tract, conjugating to form an inactive sulphate ester.

Results of animal studies show that salbutamol does not cross the blood-brain barrier.

Elimination

Systemic clearance for salbutamol is 30 litres/hour. Salbutamol is eliminated by two routes: urinary excretion of the unchanged substance and by metabolism through sulphate conjugation. The elimination half-life varies from 3 to 7 hours. Approximately 72% of the inhaled dose is excreted in urine after 24 hours, and consists of 28% unchanged drug and 44% as metabolite.

5.3. Preclinical safety data

Preclinical data based on conventional pharmacological safety, repeated dose toxicity and genotoxicity studies did not show any particular risk in humans. The teratogenicity data found in rabbits exposed to high systemic doses and the induction of benign mesovarian leiomyomas in rats are not considered of clinical importance.

6 PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Oleic acid, absolute ethanol and 1,1,1,2-tetrafluoroethane (HFA-134a).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 30ºC. Store protected from direct sunlight. Do not freeze.

6.5. Nature and contents of container

Aluminium container with 200 inhalations, each containing 100 micrograms of salbutamol, with a metering valve, actuator/mouthpiece and cap

6.6. Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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Baronesa de Maldá, 73
08950 Esplugues de Llobregat
BARCELONA – SPAIN

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)