PRODUCT MONOGRAPH

^{Pr}TEVA-SALBUTAMOL HFA

salbutamol (as salbutamol sulfate)
Inhalation Aerosol

100 mcg salbutamol per actuation
Bronchodilator

(beta$_2$-adrenergic agonist)

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[Pr]TEVA-SALBUTAMOL HFA

Salbutamol Sulfate Inhalation Aerosol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral inhalation	Inhalation aerosol/ 100 mcg salbutamol/actuation	1,1,1,2-tetrafluoroethane (HFA-134a) and Ethanol

INDICATIONS AND CLINICAL USE

Adults and Children (4 years and older):
TEVA-SALBUTAMOL HFA (salbutamol sulfate inhalation aerosol) is indicated for:

- the symptomatic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor.
- the prevention of exercise-induced bronchospasm.

Pediatrics (<4 years of age):

The safety and efficacy in children below the age of 4 years has not been established.

CONTRAINDICATIONS

TEVA-SALBUTAMOL HFA is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing (see DOSAGE FORMS, COMPOSITION AND PACKAGING)
- as a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

GENERAL

Patients should always carry their TEVA-SALBUTAMOL HFA to use immediately if an episode of asthma is experienced. If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

The bronchodilating action of sympathomimetic drugs may be antagonized by β adrenergic blocking agents with the result that the respiratory status of patients may worsen when the two drugs are used concomitantly. In patients requiring concomitant treatment with TEVA-SALBUTAMOL HFA and a β adrenergic blocking agent, the use of a relatively cardioselective β blocker (e.g. metoprolol, atenolol, acebutolol) must be considered. During the concomitant treatment, patients should be monitored carefully for possible deterioration in pulmonary function or for the need to adjust the dosage of either drug.

Excessive Use and Use with other Sympathomimetics

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. DO NOT EXCEED RECOMMENDED DOSE.

Concomitant use of TEVA-SALBUTAMOL HFA with other sympathomimetic agents is not recommended since the combined use may lead to deleterious cardiovascular effects. If concomitant use is necessary, this should take place only under strict medical supervision.

Deterioration of Asthma

Asthma may deteriorate over time. If the patient needs to use TEVA-SALBUTAMOL HFA more often than usual, this may be a sign of worsening asthma. This requires reevaluation of the patient and treatment plan and consideration of adjusting the asthma maintenance therapy. If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen (see DOSAGE AND ADMINISTRATION). It is essential that the physician instruct the patient in the need for further evaluation if the patient's asthma becomes worse.

CARDIOVASCULAR

In individual patients, any $beta_2$-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists. Care should be taken with patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension. Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST-segment depression. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin. Cardiac arrest was noticed in several instances.

ENDOCRINE AND METABOLISM

As with other beta-agonists, TEVA-SALBUTAMOL HFA may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics and by hypoxia. Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

Care should be taken with patients with diabetes mellitus. Salbutamol can induce reversible hyperglycemia during nebulised administration or especially during infusions of the drug. The diabetic patient may be unable to compensate for this and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Care should be taken with patients with hyperthyroidism.

HYPERSENSITIVITY
Immediate hypersensitivity reactions may occur after administration of salbutamol sulfate; as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, hypotension, anaphylaxis and oropharyngeal edema.

Care should be taken in patients who are unusually responsive to sympathomimetic amines.

NEUROLOGIC
Care should be taken with patients with convulsive disorders.

RESPIRATORY

Deterioration of Asthma
Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of TEVA-SALBUTAMOL HFA than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Paradoxical Bronchospasm
TEVA-SALBUTAMOL HFA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, TEVA-SALBUTAMOL HFA should be discontinued immediately and alternative therapy instituted. It should be recognized that

paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

SPECIAL POPULATIONS

Pregnant Women

Salbutamol, in common with other beta-agonists, is not approved to stop or prevent premature labour.There are no adequate and well-controlled studies in pregnant women and there is little published evidence of its safety in the early stages of human pregnancy.

Administration of any drug to pregnant women should only be considered if the anticipated benefits to the expectant woman are greater than any possible risks to the fetus (see TOXICOLOGY, Teratogenicity Studies).

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.

Labour & Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of TEVA-SALBUTAMOL HFA for relief of bronchospasm during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

TEVA-SALBUTAMOL HFA is contraindicated for the management of pre-term labour. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labour with $beta_2$-agonists, including salbutamol.

Lactating Women

Plasma levels of salbutamol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components are excreted in human milk. Because of the potential for tumorigenicity shown for salbutamol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drugs taking into account the benefit of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

Pediatrics (4 to <12 years):

The use of metered-dose inhalers in children depends on the ability of the individual child to learn the proper use of this device. Metered-dose inhalers with spacers are recommended for children under 5 years of age.

Conversion from a face mask to a mouthpiece is strongly encouraged as soon as the age and the cooperation of the child permit.

During inhalation, children should be assisted or supervised by an adult who knows the proper use of the device.

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

Pediatrics (< 4 years of age):
The safety and efficacy in children below the age of 4 years has not been established.

Geriatrics:
Clinical studies of salbutamol inhalation aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. As with other beta2-agonists, special caution should be observed when using TEVA-SALBUTAMOL HFA in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. (seeWARNINGS and PRECAUTIONS, CARDIOVASCULAR).

All $beta_2$-adrenergic agonists, including salbutamol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

MONITORING AND LABORATORY TESTS
In accordance with the present practice for asthma treatment, patient response should be monitored clinically and by lung function tests.

Monitoring Control of Asthma
Failure to respond for at least three hours to a previously effective dose of TEVA-SALBUTAMOL HFA indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose.

The increasing use of fast-acting, short duration inhaled $beta_2$-adrenergic agonists to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. In worsening asthma it is inadequate to increase $beta_2$-agonist use only, especially over an extended period of time. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other bronchodilator inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Potentially serious hypokalemia may result from beta$_2$-agonist therapy primarily from parenteral and nebulised routes of administration (see WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients. Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported usually in susceptible patients.

Other adverse reactions associated with salbutamol are nervousness and tremor. In some patients inhaled salbutamol may cause a fine tremor of skeletal muscle, particularly in the hands. This effect is common to all beta$_2$-adrenergic stimulants. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues.

In addition, salbutamol, like other sympathomimetic agents, can cause adverse effects such as drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous system stimulation, hyperactivity in children, unusual taste and drying or irritation of the oropharynx, headache, palpitations, transient muscle cramps, insomnia, nausea, weakness and dizziness.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adults and Adolescents 12 year of age and older

The adverse reaction information presented in the table below concerning TEVA-SALBUTAMOL HFA is derived from a 6-week, blinded study which compared salbutamol inhalation aerosol (200 mcg four times daily) with a double-blinded matched placebo HFA-inhalation aerosol and an evaluator-blinded marketed active comparator HFA-134a salbutamol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the salbutamol HFA inhalation aerosol treatment group and more frequently in the salbutamol HFA inhalation aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for salbutamol HFA inhalation aerosol and the marketed active comparator HFA-134a salbutamol inhaler were comparable.

Table 1: Adverse Experience Incidences (% of Patients) in a Six Week Clinical Trial*

Body System/ Adverse Event (as Preferred Term)		TEVA-SALBUTAMOL HFA (N=58)	Placebo (N=58)
Body as a Whole	Headache	7	2
Cardiovascular	Tachycardia	3	0
Musculoskeletal	Pain	3	0
Nervous System	Dizziness	3	0
Respiratory System	Pharyngitis	14	9
	Rhinitis	5	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the TEVA-SALBUTAMOL HFA group and more frequently than in placebo.

Adverse events reported by less than 3% of the patients receiving salbutamol HFA inhalation aerosol but by a greater proportion of salbutamol HFA inhalation aerosol patients than the matched placebo patients, which have the potential to be related to salbutamol HFA inhalation aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Paediatric Patients 4- to 11 years of Age:

Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of salbutamol as in salbutamol HFA inhalation aerosol (200 mcg salbutamol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

Post–Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of salbutamol HFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in post-approval use of inhaled salbutamol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, salbutamol,

like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical comment
Monoamine oxidase inhibitors or tricycle antidepressants	CS	May potentiate action of salbutamol on cardiovascular system	Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants.
Other inhaled sympathomimetic bronchodilators or epinephrine	CS	May lead to deleterious cardiovascular effects	Other inhaled sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. If additional adrenergic drugs are to be administered by any route to the patient using inhaled salbutamol, the adrenergic drugs should be used with caution. Such concomitant use must be individualized and not given on a routine basis. If regular co administration is required then alternative therapy must be considered.
Beta-blockers	CS	May effectively antagonize the action of salbutamol	Beta-adrenergic blocking drugs, especially the non-cardioselective ones, such as propranolol, should not usually be prescribed together.
Diuretics	CS	May lead to ECG changes and/or hypokalemia although the clinical significance of these effects is not known.	The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists especially when the recommended dose of the beta-agonist is exceeded. Caution is advised in the co-administration of beta agonists with non-potassium sparing diuretics.
Digoxin	CS	May lead to a decrease in serum digoxin levels, although the clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol and digoxin on a chronic bases is unclear	Mean decreases of 16-22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. It would be prudent to carefully evaluate serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

Legend: C = Case Study; CS = Class Statement; CT = Clinical Trial; T = Theoretical

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage should be individualized, and patient response should be monitored by the prescribing physician on an ongoing basis.

Increasing demand for TEVA-SALBUTAMOL HFA in bronchial asthma is usually a sign of poorly controlled or worsening asthma and indicates that the patient should be reevaluated, the treatment plan should be reviewed and the regular asthma controller treatment should be optimized If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen.

If a previous effective dosage regimen fails to provide the usual relief or the effects of a dose last for less than 3 hours, medical advice should be sought immediately; this is a sign of seriously worsening asthma that requires reassessment of therapy.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. However, if a more severe attack has not been relieved by the usual doses, additional doses may be required. In these cases, patients should immediately consult their doctors or the nearest hospital.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

Bronchospasm

For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the usual dosage is:

- ***Adolescents and adults (12 years and older):*** two inhalations (200 mcg) repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, one inhalation (100 mcg) every 4 hours may be sufficient.

  Maximum Daily Dose: Eight sprays (800 mcg)

- ***Children (4-11):*** One inhalation (100 mcg) repeated every 4 to 6 hours.. May be increased to two sprays (200 mcg salbutamol), if required.

  Maximum Daily Dose: Four sprays (400 mcg)

Exercise-Induced Bronchospasm

The usual dosage is:

- ***Adolescents and adults (12 years and older):*** two inhalations (200 mcg) 15 to 30 minutes before exercise.
- ***Children (4-11):*** one inhalation (100 mcg) 15 to 30 minutes before exercise. May be increased to two sprays (200 mcg salbutamol), if required.

DO NOT EXCEED RECOMMENDED DOSE (See WARNINGS AND PRECAUTIONS)

ADMINISTRATION
TEVA-SALBUTAMOL HFA is administered by the inhaled route only. To ensure administration of the proper dose of the drug, the patient should be instructed by the physician or other health professional in the proper use of the inhalation aerosol.

Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of drug to the lungs.

The use of open mouth technique to administer TEVA-SALBUTAMOL HFA has not been investigated in clinical trials.

Shake well before each spray. To maintain proper use of this product and to prevent medication build-up and blockage, it is important to follow the cleaning directions carefully.

Priming
Prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing three sprays into the air, away from the face.

Cleaning

As with all HFA-containing salbutamol inhalers, to maintain proper use of this product and to prevent medication build-up and blockage, it is important to keep the plastic mouthpiece clean. The inhaler may cease to deliver medication if the plastic actuator mouthpiece is not properly cleaned and dried. To clean: Wash the plastic mouthpiece with warm running water for 30 seconds, shake off excess water, and air dry thoroughly at least once a week. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage. If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, spray twice into the air away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly.

MISSED DOSE
If a single dose is missed, instruct the patient to take the next dose when it is due or if they become wheezy.

OVERDOSAGE

Signs and Symptoms
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE

REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of TEVA-SALBUTAMOL HFA Inhalation Aerosol.

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.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Treatment
Consideration should be given to discontinuation of treatment and appropriate symptomatic therapy.To antagonise the effect of salbutamol, the judicious use of a cardioselective beta-adrenergic blocking agent (e.g. metoprolol, atenolol) may be considered, bearing in mind the danger of inducing an asthmatic attack. Serum potassium levels should be monitored. There is insufficient evidence to determine if dialysis is beneficial for overdosage of salbutamol sulfate inhalation aerosol.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

For management of a suspected overdose, contact your poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of bronchial muscle fibres. This action is manifested by an improvement in pulmonary function as demonstrated by spirometric measurements. At therapeutic doses, salbutamol has little action on the $beta_1$-adrenergic receptors in cardiac muscle.

A measurable decrease in airway resistance is typically observed 5 to 15 minutes after inhalation of salbutamol. The maximum improvement in pulmonary function usually occurs 60 to 90

minutes after salbutamol treatment, and significant bronchodilator activity has been observed to persist for 3 to 6 hours.

PHARMACOKINETICS

The systemic levels of salbutamol are low after inhalation of recommended doses. In a crossover study conducted in healthy males and female volunteers, high cumulative doses of salbutamol (1.080 mcg of salbutamol base administered over one hour) yielded mean peak plasma concentrations (C_{max}) and systemic exposure (AUC_{inf}) of approximately 4,100 pg/mL and 28,426 pg/mL* hr, respectively compared to approximately 3,900 pg/mL and 28,395 pg/mL* hr, respectively following the same dose of an active HFA-134a salbutamol inhaler comparator. The terminal plasma half-life of salbutamol delivered by salbutamol HFA Inhalation Aerosol was approximately 6 hours. Comparison of the pharmacokinetic parameters demonstrated no differences between the products.

The pharmacokinetic profile of salbutamol HFA Inhalation Aerosol was evaluated in a two-way cross-over study in 11 healthy pediatric volunteers, 4 to 11 years of age. A single dose administration of salbutamol HFA Inhalation Aerosol (180 mcg salbutamol base) yielded a least square mean C_{max} and $AUC_{0-\infty}$ of 1.0 ng/mL and 307.2 ng/mL/min, respectively. The least square mean (SE) terminal plasma half-life of salbutamol delivered by Salbutamol Inhalation Aerosol was 166 minutes.

Approximately 10% of an inhaled salbutamol dose is deposited in the lungs. Eighty- five per cent of the remaining salbutamol administered from a metered-dose inhaler is swallowed, however, since the dose is low (100 to 200 mcg), the absolute amount swallowed is too small to be of clinical significance. Salbutamol is only weakly bound to plasma proteins. Results of animal studies indicate that following systemic administration, salbutamol does not cross the blood-brain barrier but does cross the placenta using an in vitro perfused isolated human placenta model. It has been found that between 2% and 3% of salbutamol was transferred from the maternal side to the fetal side of the placenta.

Salbutamol is metabolized in the liver. The principal metabolite in humans is salbutamol-o-sulfate, which has negligible pharmacologic activity. Salbutamol may also be metabolized by oxidative deamination and/or conjugation with glucuronide.

Salbutamol is longer acting than isoprenaline in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-O-methyl transferase. Salbutamol and its metabolites are excreted in the urine (>80%) and the feces (5% to 10%). Plasma levels are insignificant after administration of aerosolized salbutamol; the plasma half-life ranges from 3.8 to 7.1 hours.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (140 to 800 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was eliminated rapidly in the breath, with no evidence of metabolism or accumulation in the body. Time to maximum plasma concentration (t_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

STORAGE AND STABILITY

Keep out of the reach and sight of children. Store at a temperature between 15°C and 25°C.

SPECIAL HANDLING INSTRUCTIONS

The contents of TEVA-SALBUTAMOL HFA (salbutamol sulfate inhalation aerosol) are under pressure. The container may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Even when empty, do not puncture or incinerate container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-SALBUTAMOL HFA (salbutamol sulfate inhalation aerosol) is a pressurized metered dose inhaler (MDI) consisting of an aluminum canister fitted with a metering valve. Each canister is fitted into an actuator. A dust cap is fitted over the actuator's mouthpiece when not in use. Each spray delivers 100 mcg of salbutamol (as sulfate).

TEVA-SALBUTAMOL HFA contains an active ingredient of salbutamol sulfate and the nonmedicinal ingredients are ethanol and HFA-134a (1, 1, 1, 2-tetrafluoroethane). This product does not contain chlorofluorocarbons (CFCs) as the propellant.

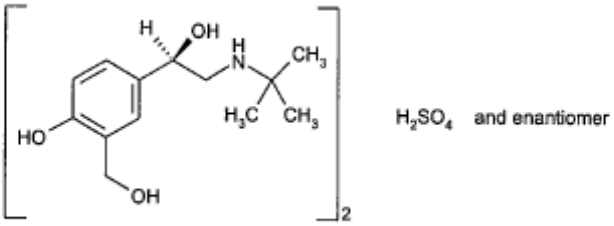
TEVA-SALBUTAMOL HFA is available in canisters of two hundred dose formats.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper Name: Salbutamol Sulfate

Structural Formula:



Molecular Formula: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$

Molecular Weight: 576.7

Chemical Name: α^1-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) salt

Physiochemical properties:

Description: Salbutamol is a white or almost white crystalline powder.

Solubility: Soluble in water and slightly soluble in chloroform and ether.

pKa Values: 9.3 and 10.3

pH values: 4.8 to 6.5 (1% aqueous solution)

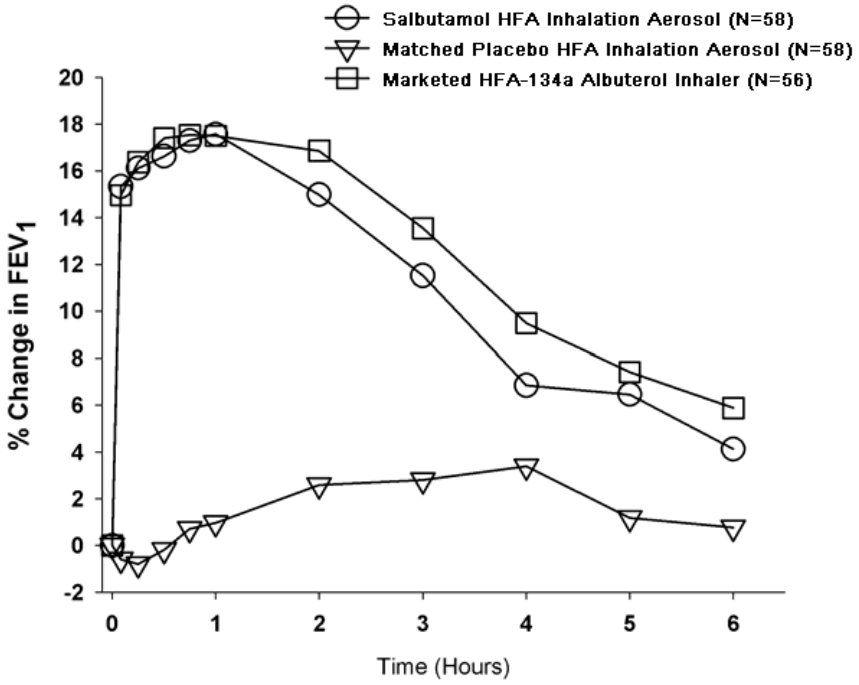
CLINICAL TRIALS

Adult and Adolescent Patients 12 Years of Age and Older: In a 6-week, randomized, double-blind, placebo-controlled trial, salbutamol HFA inhalation aerosol (58 patients) was compared to a matched placebo HFA inhalation aerosol (58 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg salbutamol four times daily. An evaluator-blind marketed active comparator HFA-134a salbutamol inhaler arm (56 patients) was included.

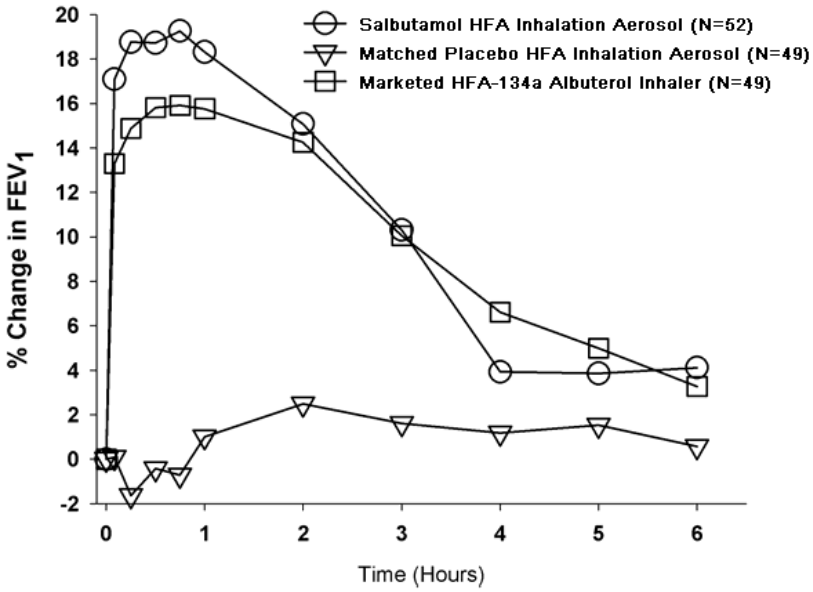
Serial FEV_1 measurements, shown below as percent change from test-day baseline at Day 1 and at Day 43, demonstrated that two inhalations of salbutamol HFA inhalation aerosol produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo, as well as a comparable bronchodilator effect to the marketed active comparator HFA-134a salbutamol inhaler.

FEV_1 as Mean Percent Change from Test-Day Pre-Dose in a 6-Week Clinical Trial

Day 1



Day 43



In this study, 31 of 58 patients treated with salbutamol HFA inhalation aerosol achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect, and median duration of effect were 8.2 minutes, 47 minutes, and approximately 3 hours, respectively. In some patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study, salbutamol HFA inhalation aerosol, administered at salbutamol doses of 100, 200 and 300 mcg, produced bronchodilator responses significantly greater than those observed with a matched placebo HFA inhalation aerosol and comparable to a marketed active comparator HFA-134a salbutamol inhaler.

Paediatric Patients 4 to 11 years of age: In a 3-week, randomized, double-blind, placebo-controlled trial, the same formulation of salbutamol as in salbutamol HFA inhalation aerosol (50 patients) was compared to a matched placebo HFA inhalation aerosol (45 patients) in asthmatic children 4 to 11 years of age at a dose of 200 mcg salbutamol four times daily. Serial FEV_1 measurements, expressed as the maximum percent change from test-day baseline in percent predicted FEV_1 at Day 1 and at Day 22 observed within two hours post-dose, demonstrated that two inhalations of HFA salbutamol sulfate produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo.

In this study, 21 of 50 pediatric patients treated with the same formulation of salbutamol as in salbutamol HFA inhalation aerosol achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. In these patients, the median time to onset, median time to peak effect and median duration of effect were 10 minutes, 31 minutes, and approximately 4 hours, respectively. In some pediatric patients, the duration of effect was as long as 6 hours.

In a placebo-controlled, single-dose, crossover study in 55 pediatric patients 4 to 11 years of age, salbutamol HFA inhalation aerosol, administered at salbutamol doses of 90 and 180 mcg, was compared with a matched placebo HFA inhalation aerosol. Serial FEV_1 measurements, expressed as the baseline-adjusted percent predicted FEV_1 observed over 6 hours post-dose, demonstrated that one and two inhalations of salbutamol HFA inhalation aerosol produced significantly greater bronchodilator responses than the matched placebo.

Exercise-Induced Bronchospasm

In a randomized, single-dose, crossover study in 24 adults and adolescents with exercise-induced bronchospasm (EIB), two inhalations of salbutamol HFA taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as maintenance of FEV1 within 80% of post-dose, pre-exercise baseline values) in 83% (20 of 24) of patients as compared to 25% (6 of 24) of patients when they received placebo.

Some of the patients who participated in this clinical trial were using concomitant inhaled or intranasal steroid therapy (no oral or injectable steroids were allowed).

DETAILED PHARMACOLOGY

Animals

In vitro studies and *in vivo* pharmacologic studies have demonstrated that salbutamol has a preferential effect on $beta_2$-adrenergic receptors compared with isoprenaline. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of $beta_2$-adrenergic receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

The pharmacologic effects of beta-adrenergic agonist drugs, including salbutamol, are at least in part attributable to stimulation through beta-adrenergie receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP). Increased cAMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

The muscle-relaxing effect of salbutamol was found to be more prolonged than when the effect was induced by isoprenaline. As suggested from the results of experiments in isolated animal tissues, salbutamol has been shown to produce a substantial bronchodilator effect in the intact animal. In the anaesthetised guinea pig, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 micrograms/kg intravenously.

Administration of salbutamol aerosol at a dose of 250 micrograms/mL for one minute to guinea pigs prevented acetylcholine-induced bronchospasm without any chronotropic effect. A prolonged bronchodilator effect of salbutamol compared to isoprenaline (in terms of mean times to dyspnea following acetylcholine challenge) was observed following oral administration of

salbutamol to conscious guinea pigs. The protective action of salbutamol in this case persisted for up to six hours.

In anaesthetised cats and dogs, salbutamol prevented the bronchospasm elicited by vagal stimulation without any significant effect on heart rate and blood pressure. Comparative tests of salbutamol and isoprenaline in isolated dog papillary muscle, guinea pig atrial muscle and human heart muscle have shown that the effect of salbutamol on $beta_1$-adrenergic receptors in the heart is minimal.

In a number of studies using guinea pig atria, it was found that on a weight-to-weight basis, salbutamol was from 2,000 to 2,500 times less active in terms of inotropic effect and 500 times less active in terms of chronotropic effect than isoprenaline. Compared to orciprenaline, salbutamol was about 40 times less active in terms of inotropic effect and four times less potent in terms of chronotropic effect. Salbutamol has been shown to be one-fifth as potent a vasodilator in skeletal muscle as isoprenaline, as measured by effects on hind limb blood flow in the anaesthetised dog. In the perfused rabbit ears salbutamol was shown to posses only one-tenth the activity of isoprenaline in terms of vasodilating effect. In dogs, salbutamol was shown to increase coronary blood flow, which was subsequently shown to be the result of a direct coronary vasodilating effect of salbutamol.

In six dogs with right-sided cardiac by-pass, salbutamol, given at the dose of' 25 micrograms/kg, improved left ventricular efficiency and increased coronary blood flow. Recent studies in minipigs, rodents, and dogs recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Animal studies show that salbutamol does not pass the blood brain barrier.

TOXICOLOGY

Acute Toxicity

Species (n)	**Oral LD_{50}**	**Intravenous LD_{50}**
Mouse (10)	>2000 mg/kg	72 mg/kg
Rat (10)	>2000 mg/kg	60 mg/kg

Rat (n)	**Intraperitoneal LD_{50}**
Newborn (155)	216 mg/kg
Weanling (100)	524 mg/kg
2 week old (90)	437 mg/kg

The rate of respiration in test animals initially increased but subsequently became abnormally slow and deep. Death, preceded by convulsions and cyanosis, usually occurred within four hours after drug administration.

Rabbits, cats and dogs survived a single dose of 50 mg/kg salbutamol.

Intermediate (Four Months) Toxicity
Rats received salbutamol twice daily, in oral doses from 0.5 to 25 mg/kg, on an increasing scale. The only significant hematological changes were a small increase in hemoglobin and packed cell volume. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at the higher dose levels.

Salbutamol was given to dogs twice daily, in oral doses from 0.05 to 12.5 mg/kg, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was depressed particularly at higher doses. Leukocyte count decreased after sixteen weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant biochemical effects were observed. The only significant histological change was the appearance of corpora amylacea in the stomach which was attributed to altered mucus secretion. Inhalation of 1000 mcg of salbutamol CFC 11/12-propelled aerosol twice daily for three months did not produce any morphological changes in the lungs, trachea, lymph nodes, liver or heart.

Long-Term Toxicity
Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for one hundred and four weeks; fifty female Charles River CD Sprague Dawley-derived rats received 20 mg/kg/day salbutamol orally for fifty weeks, and fifty female Charles River Long-Evans rats received 20 mg/kg/day salbutamol orally for ninety-six weeks. These rat studies demonstrated a dose-related incidence of mesovarian leiomyomas. No similar tumors were seen in mice.

Mutagenicity
In vitro tests involving four micro-organisms revealed no mutagenic activity.

Carcinogenicity
In a two-year study in the rat, salbutamol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and 2,800 times the maximum human inhalation dose. In another study, the effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity.

Teratogenicity Studies
Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given subcutaneously in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given subcutaneously in doses corresponding to 0.4 times the maximum human oral dose.

A reproduction study in CD-1 mice given salbutamol at doses of 0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 1.4, 14, and 140 times the maximum human aerosol dose respectively, showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. No cleft palates were observed at a dose of 0.025 mg/kg

salbutamol. Cleft palate occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoprenaline (positive control).

In rats, salbutamol treatment given orally at 0.5 2.32, 10.75 and 50 mg/kg/day throughout pregnancy resulted in no significant fetal abnormalities. However, at the highest dose level there was an increase in neonatal mortality. Reproduction studies in rats revealed no evidence of impaired fertility.

Salbutamol had no adverse effect when given orally to Stride Dutch rabbits, at doses of 0.5, 2.32 and 10.75 mg/kg/day throughout pregnancy. At a dose of 50 mg/kg/day which represents 2800 times the maximum human inhalation dose, cranioschisis was observed in 7 of 19 (37%) fetuses.

A reproduction study in New Zealand White rabbits using salbutamol sulfate/HFA 134a formulation, revealed enlargement of the frontal portion of the fontanelles in 6 of 95 (6%) and 15 of 107 (14%) fetuses at 28 and 149 mcg/kg, respectively (approximately 2/5 and 2 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis) giving plasma levels of approximately 12 and 60 ng/mL, respectively.

REFERENCES

1. Alexander DJ, Libretto SE. An overview of the toxicology of HFA-134a (1,1,1,2-tetrafluoroethane). Human & Experimental Toxicology 1995(Sep); 14(9):715-20.

2. Libretto Se. A review of the toxicology of salbutamol (salbutamol). Arch Toxicol 1994; 68:213-216.

3. Salbutamol: A review. Drugs 1971; 4:274-302.

4. PROAIR HFA Prescribing Information, US-FDA. Date of Revision: March 2012.

5. VENTOLIN HFA Health Canada Product Monograph Date of Revision: October 2, 2014

PART III: CONSUMER INFORMATION

Pr TEVA-SALBUTAMOL HFA
Salbutamol (as subutamol sulfate)
Inhalation Aerosol

This leaflet is part III of a three-part Product Monograph for TEVA-SALBUTAMOL HFA and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-SALBUTAMOL HFA. Contact your doctor or pharmacist if you have any questions about the drug. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-SALBUTAMOL HFA is used in Adults and Children 4 years or older to:

- relieve bronchospasm
- prevent bronchospasm
- prevent bronchospasm caused by exercise

Bronchospasm is a sudden worsening of shortness of breath and wheezing.

The safety and effectiveness of TEVA-SALBUTAMOL HFA in children under the age of 4 are not known.

What it does:
Salbutamol is one of a group of medicines called bronchodilators. Salbutamol relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and so helps to relieve chest tightness, wheezing and cough so that you can breathe more easily.

When it should not be used:
Do not use TEVA-SALBUTAMOL HFA:

- if you are allergic to it or any of the components of its formulation (see what the nonmedicinal ingredients are)
- for the treatment of preterm labour or miscarriage.

What the medicinal ingredient is:
salbutamol sulfate.

What the nonmedicinal ingredients is:
HFA (Hydro Fluoro Alkane) and Ethanol.

TEVA-SALBUTAMOL HFA is suspended in a CFC-free propellant.

Please note that  indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

What dosage forms it comes in:
TEVA-SALBUTAMOL HFA is supplied to you in an inhaler containing 100 mcg of salbutamol per puff.
The inhaler contains 200 puffs. The inhaler should be thrown out when 200 puffs have been used.

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-SALBUTAMOL HFA, talk to your doctor or pharmacist if you:

- have ever had to stop taking other medications for this illness because you were allergic to them or they caused problems.
- are having treatment for a thyroid condition.
- are having treatment for high blood pressure or a heart problem.
- have diabetes.
- have a past history of seizures.
- have reduced kidney function
- have low levels of potassium in your blood (hypokalemia), especially if you are taking:
    - Drugs known as xanthine derivatives (such as theophylline)
    - Steroids to treat asthma
    - Water pills (diuretics)
- are pregnant or intend to become pregnant. Taking TEVA-SALBUTAMOL HFA during pregnancy may cause harm to your baby. Your doctor will consider the benefit to you and the risk to your baby of taking TEVA-SALBUTAMOL HFA while you're pregnant.
- are breastfeeding. It is not known if TEVA-SALBUTAMOL HFA passes into breast milk.

If the relief of wheezing or chest tightness is not as good as usual, or the effect lasts for less than three hours, tell your doctor as soon as possible. If you notice a sudden worsening of your shortness of breath and wheeze shortly after taking your medicine, tell your doctor as soon as possible. It may be that your chest condition is worsening and you may need to add another type of medicine to your treatment.
You should always carry your TEVA-SALBUTAMOL HFA with you to use immediately in case you experience an asthma attack.

Effects on Children:
Children may experience:

- changes in sleep patterns
- changes in behaviour such as restlessness, excitability (hyperactivity)
- seeing or hearing things that are not there

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with TEVA-SALBUTAMOL HFA:
• Anti-depressants
• Allergy medication

• Blood pressure-lowering drugs, including propranolol
• Diuretics ("water pills")
• Bronchodilators used to open the airway (such as other asthma medication)
• Epinephrine
• Digoxin, a heart medication
• Disulfiram, a medicine used to treat alcoholism
• Metronidazole, an antibiotic medication

PROPER USE OF THIS MEDICATION

TEVA-SALBUTAMOL HFA **should only be inhaled**. Do not swallow.

If you are also using an inhaled corticosteroid:
• Always use TEVA-SALBUTAMOL HFA first
• Wait a few minutes
• Then use your inhaled corticosteroid

The effects of TEVA-SALBUTAMOL HFA should last for 4 to 6 hours.

You should call your doctor immediately if:
• the effects of one dose last less than 3 hours;
• you notice a sudden worsening of your shortness of breath
• your symptoms gets worse;
• your usual dose does not provide relief;
• you need to use TEVA-SALBUTAMOL HFA more often than before

These may be signs that your asthma or chest condition is getting worse. Your doctor may want to reassess your treatment plan

Do not increase the dose or the number of times you use your medicine without asking your doctor, as this may make you feel worse.

Usual dose:
Adults and Adolescents 12 years or older

- **To relieve and prevent bronchospasm:** 1 to 2 puffs every 4 to 6 hours as needed. If you have a more severe attack, you can repeat the dose, and immediately consult your doctor or the nearest hospital.
- **To prevent bronchospasm caused by exercise:** 2 puffs 15 minutes before exercise.
  Maximum dose – 8 puffs in a 24 hour period

Children 4-11 years

- **To relieve and prevent bronchospasm:** 1 puff every 4 to 6 hours as needed. The dose may be increased to 2 puffs if required. Follow your doctor's instructions.
- **To prevent bronchospasm caused by exercise:** 1 puff 15 minutes before exercise. The dose may be increased to 2 puffs if required. Follow your doctor's instructions.
  Maximum dose – 4 puffs in a 24 hour period

DO NOT EXCEED RECOMMENDED DOSE.

Do not increase the dose or the number of times you use TEVA-SALBUTAMOL HFA without asking your doctor, as this may make you feel worse.

If you have to go into hospital for an operation, take your inhaler with you and tell the doctor what medicine(s) you are taking.

How to Use TEVA-SALBUTAMOL HFA:
Carefully follow the instructions shown. If you have any problems, tell your doctor or pharmacist.

It is extremely important that you use your TEVA-SALBUTAMOL HFA properly to ensure that your medicine is delivered correctly so that you receive maximum benefit.

Before using TEVA-SALBUTAMOL HFA for the first time, or if your inhaler has not been used for more than 2 weeks, release four sprays into the air to ensure that it works properly.

1. Remove the cap from the mouthpiece; the strap on the cap will stay attached to the actuator, Check the mouthpiece inside and outside to ensure that it is clean.
2. Shake the inhaler vigorously.
3. Hold the inhaler upright between fingers and thumb with your thumb on the base, below the mouthpiece. Breathe out as far as is comfortable
4. Place the mouthpiece in your mouth between your teeth and close your lips around it, but do not bite it. Just after starting to breathe in through your mouth, press down on the top of the inhaler to release the drug while still breathing in steadily and deeply.
5. 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.
6. If you are to take further puffs, keep the inhaler upright and wait about half a minute before repeating steps 2 through 5.
7. After use, always snap the mouthpiece cover back into position to keep out dust and lint.

Important: Do not rush steps 3 and 4. It is important that you start to breathe in as slowly as possible just before operating your inhaler, Practice in front of a mirror for the first few times. If you see "mist" coming from the top of your inhaler or the sides of your mouth, you should start again from step 1.

If your doctor has given you different instructions for using your inhaler, please follow them carefully. Tell your doctor if you have any difficulties.

Children – TEVA-SALBUTAMOL HFA should be used under the supervision of an adult who understands the proper use of the inhaler, and only as prescribed by the doctor. The adult must encourage the child (as described above) to exhale, and then trigger the spray immediately as inhalation begins. Use of a spacer with the inhaler is recommended for children under 5 years of age. Talk to your doctor if your child has difficulties using the inhaler.

Cleaning:

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet. The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

Cleaning instructions:

- Take the canister out of the actuator, and take the cap off the mouthpiece.
- Wash the actuator through the top with warm running water for 30 seconds (see Fig. 1). Then wash the actuator again through the mouthpiece (see Fig. 2).

Figure 1

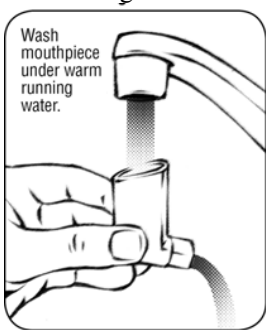
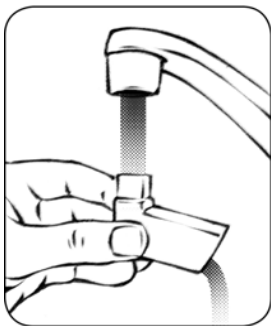
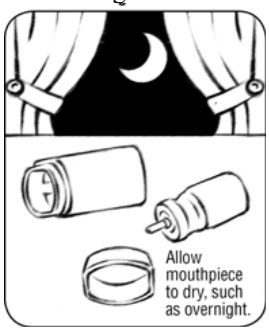


Figure 2



- Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat steps in Figures 1 and 2.
- Let the actuator air-dry completely, such as overnight (see Figure 3).

Figure 3



- When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it twice into the air away from your face. Put the cap back on the mouthpiece.

If your actuator becomes blocked:

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figures 4 and 5), wash the actuator as described in the "Cleaning Instructions" section above.

Figure 4

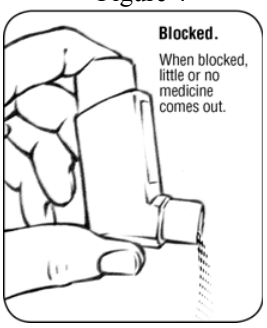
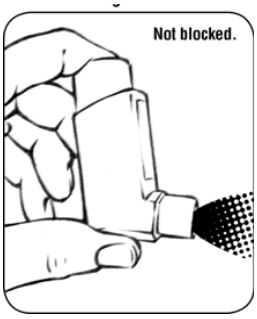


Figure 5



If you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it twice into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Take this leaflet or your medication with you so that the hospital or poison control centre will know what you have taken.

If you accidentally take a **larger dose than prescribed**, you are more likely to get side effects like a faster heart beat, headaches and feeling shaky or restless. These effects usually wear off within a few hours, but you should tell your doctor as soon as possible.

Missed Dose:

If you forget to inhale a dose, do not worry; just inhale the next dose when it is due or if you become wheezy.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

Effects on heart
• Hypertension

Effects on nervous system
• Headache
• Feeling a little shaky
• Feeling anxious or irritable
• Feeling tired or weak
• Trouble sleeping (insomnia)
• Hyperactivity in children
• Dizziness, vertigo

• Drowsiness

Effects on muscles and joints
• Muscle cramps
• Muscle pain

Other Effects
• Cough
• Respiratory infections and/or inflammation
• Diarrhea
• Nausea and vomiting
• Chest pain or discomfort
• Flushing
• Difficulty urinating
• Unusual taste in your mouth
• Dry or irritated throat

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Rare	**Bronchospasm:** Sudden worsening of shortness of breath and wheezing shortly after using TEVA-SALBUTAMOLHFA			✓
	Allergic Reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			✓
Rare	**Low Blood Potassium (hypokalemia):** muscle weakness and muscle spasms		✓	
	Hallucinations in Children: see or hear things that are not there		✓	
Unknown	Heart palpitations, faster than normal heartbeat, irregular heartbeat		✓	

This is not a complete list of side effects. If you have any unexpected effects while receiving TEVA-SALBUTAMOL HFA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of sight and reach of children.
Store at a temperature between 15°C and 25°C. Do not keep any left over medicine unless your doctor tells you to.

Warning: The canister contents are under pressure. The container may explode if heated. Do not place in hot water or near radiators, stoves or other sources of heat. Even when empty, do not puncture or incinerate container.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this leaflet again. PLEASE DO NOT THROW IT AWAY until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

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