

PRODUCT MONOGRAPH

APO-SALVENT

Salbutamol Tablets BP

2 mg and 4 mg

Bronchodilator

(Beta₂-adrenergic agonist)

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THERAPEUTIC CLASSIFICATIONBronchodilator
(Beta₂-adrenergic agonist)**ACTIONS AND CLINICAL PHARMACOLOGY**

Salbutamol produces bronchodilation through stimulation of beta₂-adrenergic receptors in bronchial smooth muscle thereby causing relaxation of muscle fibers. This action is manifested by an increase in pulmonary function as demonstrated by spirometric measurements.

A measurable decrease in airway resistance is typically observed 30 minutes after an oral dose of salbutamol sulfate. The maximum improvement in pulmonary function usually occurs after 2 to 3 hours, and significant bronchodilator activity has been observed to persist for 6 hours or longer.

A single dose of 5 mg of salbutamol orally produced an increase in FEV₁ greater than that obtained from inhalation of 200 µg of isoproterenol. The effect was sustained for more than 5 hours with an onset after 15 minutes and a peak effect at 3 hours. Salbutamol is not inactivated by catechol-O-methyl transferase and this contributes to the prolonged action of the drug.

Comparative Bioavailability

A bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of salbutamol after a single oral 8 mg dose of VENTOLIN 4 mg tablets and APO-SALVENT 4 mg tablets was measured and compared. The results are summarized as follows:

<u>Parameter</u>	Geometric Mean Arithmetic Mean (CV%)		**Ratio of Means (%)
	Apo-Salvent	Ventolin	
AUC _T (ng·hr/mL)	147 152 (29)	141 144 (24)	104.2
AUC _I (ng·hr/mL)	157 161 (24)	152 155 (22)	102.5
C _{max} (ng/mL)	23.3 25.0 (36)	20.7 21.9 (36)	112.7
T _{max} * (hr)	1.92 (0.81)	2.36 (1.10)	-
t _{1/2} * (hr)	7.06 (3.22)	6.88 (1.70)	-
For the T _{max} and t _{1/2} parameters, these are the arithmetic means (standard deviations).			
**Based on the least squares estimate of the geometric means.			

INDICATIONS AND CLINICAL USE

APO-SALVENT (salbutamol) tablets are indicated for the symptomatic chronic relief and prevention of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor. APO-SALVENT tablets should be used regularly.

CONTRAINDICATIONS

Hypersensitivity to salbutamol or to any of the ingredients, and in patients with cardiac tachyarrhythmias. APO- SALVENT (salbutamol) tablets are not to be used for relief of acute bronchospasm or for use in children under 6 years of age. Apo-Salvent tablets are contraindicated in patients at risk of threatened abortion.

WARNINGS

In accordance with the present practice for asthma treatment, concomitant anti-inflammatory therapy should be part of the regimen if salbutamol needs to be used on a regular daily basis.

Endocrine and Metabolism

In common with other β -adrenergic agents, salbutamol can induce reversible metabolic changes. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and hypoxia. Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias (see PRECAUTIONS). It is recommended that serum potassium levels be monitored in such situations.

Care should be taken with patients with diabetes mellitus or with hyperthyroidism.

Cardiovascular

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.

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 individual patients, any beta 2-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect.

Salbutamol should be administered with extreme caution to patients being treated with MAO inhibitors or tricyclic antidepressants since the action of salbutamol on the cardiovascular system may be potentiated.

Hypersensitivity

Immediate hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal edema and collapse have been reported very rarely.

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

Neurologic:

Care should be taken with patients with convulsive disorders.

Pregnancy and Lactation:

Salbutamol is not approved to stop or prevent premature labour. The safety of salbutamol in pregnancy and in lactation has not been established.

PRECAUTIONS

Increasing use of β_2 -agonists is usually a sign of worsening asthma. Under these conditions it is inadequate simply to increase their use, in particular over an extended period of time, and a reassessment of the patient's therapy plan is required and concomitant anti-inflammatory therapy should be considered.

Drug Interactions:

APO-SALVENT (salbutamol) tablets should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants since the action of salbutamol on the cardiovascular system may be potentiated.

Beta-adrenergic blocking drugs, especially the non-cardioselective ones, may effectively antagonize the action of salbutamol.

The concomitant use of salbutamol and other sympathomimetic agents or epinephrine is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving salbutamol tablets. Such concomitant use should be individualized, and not given on a routine basis. If regular co-administration is required, then this may indicate that disease control is suboptimal and alternative therapy should be considered.

Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics (such as loop or thiazide diuretics). Beta-agonists have been associated with reductions in serum potassium levels. The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.

Co-administration of salbutamol with digoxin 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 basis is unclear.

Pregnancy:

Teratogenic Effects: Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; however as with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy. In animal studies there was evidence of some harmful effects on the fetus at very high dose levels. Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given s.c. in doses corresponding to the human nebulization dose; when given s.c. in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given s.c. in doses corresponding to 0.4 times the maximum human oral dose.

Labour and Delivery:

There are no adequate and well-controlled studies in pregnant women. Salbutamol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral salbutamol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labour or prevent labor at term. Therefore, cautious use of APO-SALVENT tablets is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

There is insufficient evidence to support use of oral beta 2-agonists for prevention of premature delivery. No statistically significant effect on perinatal mortality to morbidity has been observed in controlled trials. Further, maternal pulmonary edema and myocardial ischemia have been reported during or following premature labour in patients receiving beta 2-agonists.

Lactation:

As salbutamol is probably secreted in breast milk and because of the potential for tumorigenicity shown in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

ADVERSE REACTIONS

The most frequent adverse reactions to salbutamol are nervousness and tremor. Salbutamol may cause a fine tremor of the skeletal muscle in some patients; usually the hands are most obviously affected. This is common to all beta-adrenergic stimulants. Adaptation occurs in the first few days of the dosing and in most cases disappears as treatment continues.

Headache, tension due to effects on skeletal muscle, tachycardia, palpitations, transient muscle cramps, insomnia, nausea, weakness, dizziness and sweating have also been reported. Other rare adverse reactions have been drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.

In patients who are unusually sensitive to beta-adrenergic stimulants, peripheral vasodilation and a compensatory small increase in heart rate may occur.

As with other β_2 -agonists, hyperactivity has been reported rarely in children.

Potentially serious hypokalemia may result from β_2 -agonist therapy, mainly from parenteral and nebulized administration.

Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension, rash, oropharyngeal edema and collapse have been reported very rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Overdosage may cause tachycardia, cardiac arrhythmias, hypokalemia, hypertension and in extreme cases, sudden death.

Following oral overdosage, peripheral vasodilation and increased irritability of skeletal muscle, hypokalemia, tachycardia, cardiac arrhythmia, hypertension may occur. In case of oral overdose, gastric lavage should be performed.

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:

To antagonize 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.

DOSAGE AND ADMINISTRATION

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

Administer dosage 3 to 4 times daily. Children: 6 to 12 years of age, 2 mg; over 12 years of age, 2 to 4 mg. Adults: 2 to 4 mg.

Salbutamol tablets are not intended for patients experiencing an acute episode of bronchospasm and are not to be used in children under 6 years of age.

In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 2 mg 3 or 4 times daily.

The total daily dose should not exceed 16 mg (adults and children over 12 years of age) or 8 mg (children 6 to 12 years of age). Dosage may be adjusted from this initial level according to individual patient response: a fine skeletal muscle tremor which is dose related and caused by a direct skeletal muscle effect, not CNS stimulation, may be encountered in a few cases. If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that could require reassessment of therapy.

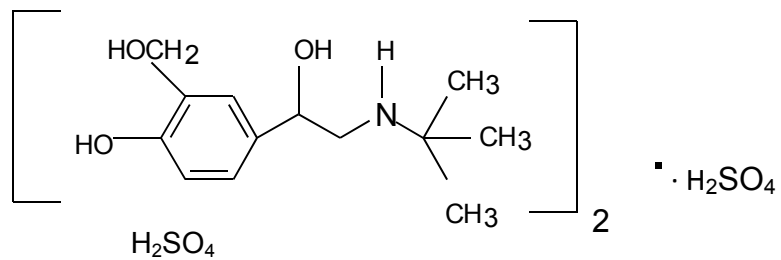
When prescribed APO-SALVENT (salbutamol) tablets, the patient should be advised that the action of this medication may last for 6 to 8 hours. As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased upon medical advice.

PHARMACEUTICAL INFORMATION**Drug Substance**

Proper/Common Name: Salbutamol sulfate

Chemical Name(s): 2-t-butylamino-1-(4-hydroxy-3-hydroxymethyl) phenylethanol sulfate

Structural Formula:



Molecular Formula : (C₁₃H₂₁NO₃)₂ ·

Molecular Weight: 576.7

Composition

APO-SALVENT tablets contain salbutamol sulfate equivalent to 2 mg and 4 mg of salbutamol. In addition to the salbutamol sulfate, each tablet contains the non-medicinal ingredients lactose, microcrystalline cellulose, starch, magnesium stearate, D&C red #30 and ferric-ferrous oxide.

Stability and Storage Recommendations

Store at controlled room temperature 15-30 °C (59-86 °F).

AVAILABILITY OF DOSAGE FORMS

APO-SALVENT TABLETS 2 mg are light purple, round, flat-faced with bevelled edge tablets, scored and engraved APO over 2 on one side, containing salbutamol sulfate equivalent to 2 mg of salbutamol. Available in bottles of 100, 500 and 1000.

APO-SALVENT TABLETS 4 mg are light purple, round, flat-faced with bevelled edge tablets, scored and engraved APO over 4 on one side, containing salbutamol sulfate equivalent to 4 mg of salbutamol. Available in bottles of 100, 500 and 1000.

ANIMAL PHARMACOLOGY

Salbutamol has a relatively selective action on the beta₂-adrenergic receptors of the bronchial and vascular smooth muscles. In anesthetized guinea pigs, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 mcg/kg intravenously.

In anesthetized dogs, salbutamol is one-fifth as potent as isoprenaline in skeletal muscle vasodilation.

In the isolated atrium preparation of guinea pigs, salbutamol was 525 times less potent than isoprenaline in increasing the rate and force of contraction, respectively.

Administration of salbutamol aerosol at the dose of 250 mcg/mL for one minute to guinea pigs, prevented acetylcholine-induced bronchospasm without any effect on the heart rate.

In anesthetized 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-adrenergic receptors in the heart is minimal.

In 6 dogs with right-sided cardiac bypass, salbutamol, given at the dose of 25 mcg/kg, improved left ventricular efficiency and increased coronary blood flow.

CLINICAL PHARMACOLOGY

In a trial involving 12 patients, daily measurements of peak expiratory flow rate showed improvement in 8, no change in 3, and worsening in one case during treatment with salbutamol tablets.

A single dose of 5 mg of salbutamol orally produced an increase in FEV₁ greater than that obtained from inhalation of 200 mcg of isoprenaline. The effect was sustained for more than 5 hours with an onset after 15 minutes and a peak effect at 3 hours. Salbutamol is not inactivated by catechol-O-methyl transferase and this contributes to the prolonged action of the drug.

Following oral administration of tritiated salbutamol sulfate to man, peak plasma levels were attained within 2.5 hours and declined with a terminal half-life of 3 to 5 hours. Roughly 70% of the administered dose was excreted in the urine within 24 hours.

Salbutamol sulfate, administered orally to healthy volunteers in a dose of 4 mg, raised plasma levels of insulin, glucose, and non-esterified fatty acids, had no effect on triglyceride levels, and lowered serum potassium.

METABOLISM

It was found in asthmatic patients that salbutamol, administered orally, by aerosol, or intravenously, was metabolized to its 4'-o-sulfate ester. Both free salbutamol and the metabolite were excreted in the urine, the ratio of the two varying with the route of administration and suggesting that metabolism occurred in the gut and/or the liver. Pharmacological testing showed that the metabolite had negligible beta-adrenoceptor stimulant and no blocking activity.

TOXICOLOGY

Acute:

Oral LD₅₀

Animal Species	Sex	LD₅₀ (and 95% probability inclusive of the 20% confidence limits) mg/kg.
Albino Mice*	F	2500 (1793-3486)
	M	3750 (3271-4299)
	Combined	3300 (2900-3755)
Albino Rats**	Combined	>5000

* 6 groups, each with 5 mice/sex, were treated with the test article, salbutamol sulfate, at logarithmically spaced doses.

** 1 group of 5 rats/sex were treated with a single dose of the test article of 5000 mg/kg.

Mortality generally occurred over a 4 hour period post-dosing in mice; only one male rat died approximately 24 hours post-dosing.

Systemic toxicity was generally characterized by tonic convulsions, cyanosis, dyspnea, reduced activity, shallow breathing, tremors, hunched back, piloerection and ptosis.

Necropsy of these animals generally demonstrated distention of the stomach or intestines, paleness of the kidneys or liver, occasionally pulmonary congestion or irritation of the gastrointestinal mucosa. Animals killed routinely at the completion of the study revealed no grossly visible tissue changes.

Intravenous LD₅₀

Mouse	(10)	72 mg/kg
Rat	(10)	60 mg/kg

Intraperitoneal LD₅₀ in Rat (Number of animals in brackets)

Newborn	(155)	216 mg/kg
Weanling	(100)	524 mg/kg
Six Week Old	(90)	427 mg/kg

Animals which died had convulsions and cyanosis. Death occurred mostly within 4 hours after administration. Respiration first increased, then decreased to abnormally slow and deep.

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

Intermediate (Four Months)

RAT:

When salbutamol was given p.o. from 0.5 mg/kg up to 25 mg/kg daily on an increasing scale, there were no significant hematological changes except a small increase in hemoglobin and packed cell volumes. 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 higher dose levels.

DOGS:

Dosage of 0.05 mg/kg up to 12.5 mg/kg p.o. daily on an increasing scale resulted in a depressed rate of increase of hemoglobin and packed cell volume, particularly at higher doses. Leukocyte count decreased after 16 weeks of treatment at each dose level. Platelet count was increased after 8 weeks at the highest dose.

No significant effects were seen on biochemical values. The only significant histological change was the appearance of corpora amylacea in the stomach, attributed to altered mucous secretion.

Inhalation of 1000 mcg of salbutamol aerosol for 3 months produced no morphological changes in lungs, trachea, lymph nodes, liver and heart.

Long-term:

Chronic toxicity studies were carried out in 2 separate centres. Fifty female, Charles River CD albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for 104 weeks; 50 female Charles River CD Sprague-Dawley derived rats received orally 20 mg/kg/day for 50 weeks, and 50 female Charles River Long-Evans rats received orally 20 mg/kg/day for 96 weeks. These studies demonstrated a dose-related incidence of mesovarian leiomyomas. No similar tumors were seen in mice. There was no evidence of any carcinogenic effect in any species tested and in vitro tests involving 4 different micro-organisms revealed no mutagenic activity.

TERATOGENIC STUDIES

RAT:

No adverse effect was seen when salbutamol was given orally at 0.5, 2.32, 10.75 and 50 mg/kg/day throughout pregnancy. When given to 2 consecutive generations at doses up to 50 mg/kg/day, no adverse effect was observed on the reproductive function of either male or female rats. The only toxic effect was an increase in neonatal mortality in the highest dose level group.

All the progeny that died showed obvious signs of lack of parental care.

RABBIT:

Given orally at 0.5, 2.32, and 10.75 mg/kg/day doses throughout pregnancy, salbutamol had no adverse effect.

At the dose of 50 mg/kg/day, it inhibited the weight gain of the does.

Salbutamol had no teratogenic action under these experimental conditions.

BIBLIOGRAPHY

1. Brittain RT, Farmer JB, Jack D, Martin LE, Simpson WT. AH.3365: a selective β -adrenergic stimulant. *Nature* 1968; 219: 862-863.
2. Cochrane GM, Clark TJH, Hanan ME. The role of oral bronchodilator therapy as shown by a comparison between salbutamol and terbutaline. *Curr Med Res Opin* 1973; 1: 517-523.
3. Connolly NM. Dosage of oral salbutamol in asthmatic children. *Arch Dis Child* 1971; 46: 869-871.
4. Cullum VA, Farmer JB, Jack D, Levy GP. Salbutamol: a new selective β -adrenoceptive receptor stimulant. *Br J Pharmacol* 1969; 35: 141-151.
5. Epstein SW, Barnard JA, Zsoter TT. A clinical trial of long-term oral salbutamol in reversible diffuse airway obstruction. *Am Rev Resp Dis* 1973; 108: 1367-1372.
6. Evans ME, Walker SR, Brittain RT, Paterson JW. The metabolism of salbutamol in man. *Xenobiotica* 1973; 3: 113-120.
7. Grimwood K, Jonnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalation powder or nebulizer? *Br Med J* 1981; 282: 105-106.
8. Kamburoff PL, Prime FJ. Oral and inhaled salbutamol as a bronchodilator. *Br J Dis Chest* 1970; 64: 46-54.
9. Larsson S, Svedmyr N. Bronchodilating effect and side effects of beta₂-adrenoceptor stimulants by different modes of administration (tablets, metered aerosol, and combinations thereof). A study with salbutamol in asthmatics. *Am Rev Resp Dis* 1977; 116: 861-869.
10. Legge JS, Gaddie J, Palmer KNV. Comparison of two oral selective β ₂-adrenergic stimulant drugs in bronchial asthma. *Br Med J* 1971; 1: 637-639.
11. Parker SS, Choo-Kang YFJ, Cooper EJ, Cameron SJ, Grant IWB. Bronchodilator effect of oral salbutamol in asthmatics treated with corticosteroids. *Br Med J* 1971; 4: 139-142.
12. Powell ML, Weisberger M, Gural R, Chung M, Patrick JE, Radwanski E, Symchowicz SS. Comparative bioavailability and pharmacokinetics of three formulations of albuterol. *J Pharmaceut Sci* 1985; 74: 217-219.
13. Taylor MW, Gaddie J, Murchison LE, Palmer KNV. Metabolic effects of oral salbutamol. *Br Med J* 1976; 1: 22

14. Vulliemoz Y, Verosky M, Triner L. Effect of albuterol and terbutaline, synthetic beta-adrenergic stimulants, on the cyclic 3', 5'-adenosine monophosphate system in smooth muscle. *J Pharm Exp Ther* 1975; 195: 549-556.
15. Walker SR, Evans ME, Richards AJ, Paterson JW. The clinical pharmacology of oral and inhaled salbutamol. *Clin Pharmacol Ther* 1972; 13: 861-867.
16. Warrell DA, Robertson DG, Newton Howes J, Connolly ME, Paterson JW, Beilin LJ, Dollery CT. Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. *Br Med J* 1970; 1: 65-70.