PRODUCT MONOGRAPH

phl-SALBUTAMOL ORAL LIQUID

(Salbutamol Sulphate Solution)

Oral Liquid, 0.4 mg/mL

Bronchodilator
(beta$_2$-adrenergic stimulant)

PHARMEL INC.
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Date of Preparation:
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Control No. 095317

PRODUCT MONOGRAPH

NAME OF DRUG

phl-SALBUTAMOL ORAL LIQUID
(Salbutamol Sulphate Solution)

THERAPEUTIC CLASSIFICATION

Bronchodilator, $beta_2$-adrenergic stimulant

CLINICAL PHARMACOLOGY

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.

A measurable decrease in airway resistance is typically observed 30 minutes after an oral dose of salbutamol sulphate. 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.

INDICATIONS AND CLINICAL USE

Prevention or relief of bronchospasm due to bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients and in patients with tachyarrhythmias. Salbutamol Sulphate Oral Liquid is not recommended in children under two years of age, until the dosage regimen and evidence concerning its safety have been established.

WARNINGS

USE OF ANTI-INFLAMMATORY AGENTS: 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 (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.

DETERIORATION OF ASTHMA: The management of asthma should normally follow a stepwise program and patient response should be monitored clinically and by lung function tests. 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. 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.

CARDIOVASCULAR EFFECTS: In individual patients, any $beta_2$-adrenergic agonist, including salbutamol, may have a clinically significant cardiac effect. 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.

HYPOKALEMIA: In common with other beta-adrenergic agents, salbutamol can induce reversible metabolic changes such as potentially serious hypokalemia, particularly following nebulised or especially infused administration. Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids, 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.

DIABETES: Care should be taken with patients with diabetes mellitus. Salbutamol can induce reversible hyperglycemia during oral or nebulized 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.

IMMEDIATE HYPERSENSITIVITY REACTIONS: Immediate hypersensitivity reactions may occur after administration of salbutamol or salbutamol sulphate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, hypertension, anaphylaxis and oropharyngeal edema.

DO NOT EXCEED RECOMMENDED DOSE: Fatalities have been reported following 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. Therefore, it is essential that the physician instruct the patient in the need for further evaluation in case of deterioration.

Care should be taken with patients suffering from convulsive disorders, hyperthyroidism or in patients who are unusually responsive to sympathomimetic amines.

OTHERS: Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of salbutamol sulfate in children.

PRECAUTIONS

GENERAL

If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought in order to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately.

Failure to respond to a previously effective dose of salbutamol 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 $beta_2$-agonists to control symptoms is usually a sign of worsening asthma. In worsening asthma it is inadequate to increase $beta_2$-agonists use only, especially over an extended period of time. Instead, a reassessment of the patient's therapy plan is required and concomitant anti-inflammaory therapy should be considered (see DOSAGE AND ADMINISTRATION).

Patients should be advised to always carry their salbutamol aerosol or drug powder inhaler to use immediately if an episode of asthma is experienced.

USE IN WOMEN

Pregnant Women

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence. However, 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 drugs during pregnancy should only be considered if the anticipated benefits to the expectant woman are greater than any possible risks to the fetus.

A reproduction study in CD-1 mice with salbutamol 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. None was observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol positive control. A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 78 times the maximum human oral dose of salbutamol.

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 and Delivery

Oral salbutamol has been shown to delay preterm labour in some reports, but there are no well-controlled studies which demonstrate that it will stop preterm labour or prevent labour at term. Therefore, cautious use of salbutamol sulphate oral liquid is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractility.

Lactating Mothers

Since salbutamol is probably excreted in breast milk and because of its observed tumorigenicity in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

DRUG INTERACTIONS

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

Other sympathomimetic bronchodilators or epinephrine: Other 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 salbutamol, the adrenergic drugs should be used with caution to avoid deleterious cardiovascular effects. 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: Beta-adrenergic blocking drugs, especially the non-cardioselective ones, may effectively antagonise the action of salbutamol, and therefore salbutamol and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

Diuretics: 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. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

Digoxin: Mean decreases of 16-22% in serum digoxin levels were demonstrated after single doses intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airways disease who are receiving salbutamol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

ADVERSE REACTIONS

The most frequent adverse reactions are nervousness and tremor. In some patients, phl-SALBUTAMOL ORAL LIQUID 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. A few patients experience a feeling of tension; this is also due to the effects on the skeletal muscle and not to direct CNS stimulation. Headache, tachycardia, palpitations, muscle cramps, insomnia, nausea, weakness and dizziness have also been reported.

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

Rarely reported adverse effects include 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.

Immediate hypersensitivity reactions including angiodema, urticaria, bronchospasm, hypotension, rash, oropharyngeal oedema, anaphylaxis and collapse have been reported very rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage may cause, peripheral vasodilation and increased irritability of skeletal muscle, hypokalemia, tachycardia, arrhythmia, hypertension and, in extreme cases, sudden death. In case of overdosage, gastric lavage should be performed. In order to antagonize the effect of salbutamol, the use of a beta-adrenergic blocking agent preferably one of the relatively cardioselective ones (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. If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately; this is a sign of seriously worsening asthma that could require reassessment of therapy.

In accordance with the present practice for asthma treatment, if salbutamol is required for relief of symptoms more than twice a day on a regular daily basis or for an extended period of time, anti-inflammatory therapy (e.g. corticosteroid) should be part of the regimen.

phl-SALBUTAMOL ORAL LIQUID is not intended for patients experiencing an acute episode of bronchospasm. Patients should always carry their salbutamol aerosol or dry powder inhaler to use immediately if an episode of asthma is experienced.

When phl-SALBUTAMOL ORAL LIQUID is prescribed, 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.

phl-SALBUTAMOL ORAL LIQUID is not used in children under two 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 5 mL (2 mg) three or four times per day.

Adults and children over 12 years of age: 5 to 10 mL (2 to 4 mg) 3 to 4 times daily.

Children (6 and 12 years of age): 5 mL (2 mg) 3 to 4 times daily.

Children (2 to 6 years of age): 0.25 mL (0.1 mg) per kg body weight 3 to 4 times daily.

The safety and efficacy of phl-SALBUTAMOL ORAL LIQUID in children under 2 years of age, and for chronic therapy in children 2 - 6 years of age have not been established.

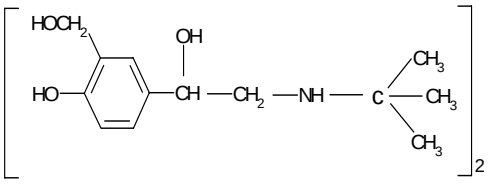
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Salbutamol sulphate

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

Structural Formula:



H_2SO_4 *Molecular Formula*: $[C_{13}H_{21}NO_3]_2H_2SO_4$

Molecular Weight: 576.71

Physical Form: Salbutamol sulphate is white or almost white powder. It is odourless or almost odourless.

Solubility: Salbutamol sulphate is soluble in 4 parts of water; slightly soluble in ethanol (96%), in chloroform and in ether.

pH and pKa: A 5% solution of salbutamol sulphate in distilled water has a pH value of 4.3. Salbutamol has pKa values of 9.3 and 10.3.

Distribution Coefficient: The distribution coefficient of salbutamol between two phases of octanol and water, as determined by HPLC, is log D=-0.5 at pH 7.42 at room temperature.

Melting Point: Salbutamol melts at approximately 155˚C, with decomposition

Composition:

phl-SALBUTAMOL ORAL LIQUID contains salbutamol sulphate and the following excipients: citric acid monohydrate, hydroxypropyl methylcellulose, orange extract, purified water, sodium benzoate, sodium citrate dihydrate and sodium cyclamate.

Storage Recommendations:

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

AVAILABILITY OF DOSAGE FORMS

phl-SALBUTAMOL ORAL LIQUID is a clear, colourless, orange-flavoured liquid containing 0.4 mg salbutamol per mL. phl-SALBUTAMOL ORAL LIQUID is available in high density polyethylene bottles of 250 mL and 500 mL. The bottles are closed with white polypropylene caps lined with pulp and vinyl.

PHARMACOLOGY

Animal studies

Salbutamol has a relatively selective action of salbutamol on the $beta_2$-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 500 to 2500 times less potent than isoprenaline in increasing the rate and force of contraction, respectively.

Administration of salbutamol aerosol at a 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/mL, improved left ventricular efficiency and increased coronary blood flow.

Human Studies

A single dose of 5 mg of salbutamol orally produced an increase of FEV_1 greater than that obtained from inhalation of 200 mcg of isoprenaline. The effect was sustained for more than five hours with an onset after fifteen minutes and a peak effect at three 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 sulphate 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 sulphate, 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.

It was found in asthmatic patients that salbutamol, administered orally, by aerosol, or intravenously, was metabolized to its 4'-o-sulphate 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 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
6-weeks (90)	437 mg/kg

(number of animals in brackets)

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 oral dose of 50 mg/kg salbutamol.

Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden deaths (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. the significance of these findings when applied to humans is concurrently unknown.

Intermediate (Four Months) Toxicity

Rats: Salbutamol was given in oral doses from 0.5 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: Salbutamol was given in oral doses from 0.05 up to 12.5 mg/kg daily, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was depressed, 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 which was attributed to altered mucus secretion. Inhalation of 1000 μg of salbutamol aerosol for 3 months did not produce any morphological changes in lungs, trachea, lymph nodes, liver and heart.

Long-term Toxicity

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 20 mg/kg/day salbutamol orally for 50 weeks, and 50 female Charles River Long-Evans rats received 20 mg/kg/day salbutamol orally for 96 weeks. These studies demonstrated a dose-related incidence of mesovarium leiomyomas. No similar tumors were seen in mice.

Mutagenicity

In-vitro tests involving 4 different micro-organisms revealed no mutagenic activity.

Carcinogenicity

In a two-year study in the rat, salbutamol sulphate 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 coadministration of propranolol. The relevance of these findings to human 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 the 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 doses 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 was 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.

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