Pharmaniaga Terbutaline Respirator Solution

DESCRIPTION
Clear, colourless to yellow solution.

COMPOSITION
Each mL contains Terbutaline Sulphate 10 mg and Benzalkonium Chloride 0.01% w/v (as preservative)

PHARMACODYNAMICS
Pharmacotherapeutic group: selective beta$_2$-adrenoreceptor agonists, terbutaline, ATC code: R03A C03.

Terbutaline is a selective beta$_2$-adrenergic stimulant, having the following pharmacological effects:

i) In the lung: bronchodilation; increase in mucociliary clearance; suppression of oedema and anti-allergic effects.
ii) In skeletal muscle: stimulates Na^+/K^+ transport and also causes depression of subtetanic contractions in slow-contracting muscle.
iii) In uterine muscle: Inhibition of uterine contractions.
iv) In the C.N.S: Low penetration into the blood-brain barrier at therapeutic doses, due to the highly hydrophilic nature of the molecule.
v) In the C.V.S.: Administration of terbutaline results in cardiovascular effects mediated through beta$_2$-receptors in the peripheral arteries and in the heart e.g. in healthy subjects, 0.25 - 0.5 mg injected s.c., is associated with an increase in cardiac output (up to 85% over controls) due to an increase in heart rate and a larger stroke volume. The increase in heart rate is probably due to a combination of a reflex tachycardia, via a fall in peripheral resistance, and a direct positive chronotropic effect of the drug.

PHARMACOKINETICS
Basic parameters have evaluated in man after i.v. and oral administration of therapeutic doses, e.g.

I.V. single dose
Volume distribution (VSS) - 114L
Total body clearance (CL) - 213 ml/min.
Mean residence time (MRT) - 9.0 h.
Renal clearance (CLR) - 149 ml/min.(males)

Oral dose
Renal clearance (CLR) - 1.925 ml/min. (males)
Renal clearance (CLR) - 2.32 ml/min. (females)

The plasma concentration/time curve after i.v. administration is characterised by a fast distribution phase, an intermediate elimination phase and a late elimination phase.

Terminal half-life t½ has been determined after single and multiple dosing (mean values varied between 16-20 h.).

Bioavailability
Food reduces bioavailability following oral dosing (10% on average) fasting values of 14-15% have been obtained.

Metabolism
The main metabolite after oral dosing is the sulfate conjugate and also some glucoronide conjugate can be found in the urine.

INDICATIONS
Terbutaline is a selective beta2-adrenergic agonist recommended for the relief of severe bronchospasm in bronchial asthma and in chronic bronchitis and other bronchopulmonary disorders in which bronchospasm is a complicating factor.

CONTRAINDICATIONS
Contraindicated in patients with a history of hypersensitivity to terbutaline.

ADVERSE REACTIONS
Summary of safety profile

The frequency of adverse reactions is low at the recommended dose. Terbutaline given by inhalation is unlikely to produce significant systemic effects when given in recommended doses. Most of the adverse reactions are characteristic of sympathomimetic amines. The majority of these effects have reversed spontaneously within the first 1-2 weeks of treatment. The frequency of side-effects is low at the recommended doses.

Tabulated list of adverse reaction

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class (SOC)	Frequency Classification	Adverse Drug Reaction Preferred term (PT)
Immune system disorders	Not known^	Hypersensitivity reactions including angioedema, bronchospasm, hypotension and collapse
Metabolism and nutritional disorders	Common	Hypokalaemia
	Not known^	Lactic acidosis
Psychiatric disorders	Not known^	Sleep disorder and Behavioural disturbances, such as agitation and restlessness
Nervous system disorders	Very Common	Tremor Headache
Cardiac disorders	Common	Tachycardia Palpitations
	Not known^	Arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles Myocardial ischaemia
Vascular disorders	Not known^	Peripheral vasodilation
Respiratory, thoracic and mediastinal disorders	Not known^	Paradoxical bronchospasm*
Gastrointestinal disorders	Not known^	Nausea Mouth and throat irritation
Skin and subcutaneous tissue disorders	Not known^	Urticaria Rash
Musculoskeletal and connective tissue disorders#	Common	Muscle spasms

A few patients feel tense; this is also due to the effects on skeletal muscle and not to direct CNS stimulation.
^ Reported spontaneously in post-marketing data and therefore frequency regarded as unknown.
* In rare cases, through unspecified mechanisms, paradoxical bronchospasm may occur, with wheezing immediately after inhalation. This should be immediately treated with a rapid-onset bronchodilator. Terbutaline therapy should be discontinued and after assessment, an alternative therapy initiated.

WARNINGS AND PRECAUTIONS
Patients should be instructed in proper use and their inhalation technique checked regularly.

Patient who are prescribed regular anti-inflammatory therapy should be advised to continue taking their anti-inflammatory medication even when symptoms decrease and they do not require Terbutaline.

If a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should seek medical advise as soon as possible as this could be a sign of worsening asthma and warrants a reassessment of the asthma therapy.

Patients with persistent asthma who require maintenance therapy with beta 2-agonists should also receive optimal anti-2 inflammatory therapy e.g. inhaled corticosteroids, leukotriene receptor antagonists. These patients must be advised to continue taking their anti-inflammatory therapy after the introduction of Terbutaline even when symptoms decrease. Should symptoms persist, or if treatment with beta 2-agonists needs to be increased, this indicates a worsening of the underlying 2 condition and warrants a reassessment of the therapy. Consideration should be given to the requirements for additional therapy (including increased dosages of anti-inflammatory medication). Severe exacerbations of asthma should be treated as an emergency in the usual manner.

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.

Patients who take more than twice a week additional “as needed” terbutaline should be re-evaluated for proper treatment adjustment as these patients are at risk for overuse of terbutaline.

As for all beta 2-agonists caution should be observed in patients with thyrotoxicosis.

Due to the positive inotropic effect of the beta 2-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Cardiovascular effects may be seen with sympathomimetic drugs, including Terbutaline. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta-agonists. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving terbutaline should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Due to the hyperglycaemic effects of beta 2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from beta 2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments. It is recommended that serum potassium levels are monitored in such situations.

Lactic acidosis has been reported in association with high therapeutic doses of parenteral and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation. In patients not adequately responding to acute Terbutaline therapy, consideration should be given to the presence of lactic acidosis as a possible contributing factor to ongoing respiratory symptoms.

Pregnancy:
Although no teratogenic effects have been observed in animals or in patients, Terbutaline should only be administered with caution during the first trimester of pregnancy.
If used in maintenance therapy for asthma and other pulmonary diseases, Terbutaline should be used with caution at the end of pregnancy because of the potential tocolytic effect.

Breast-feeding:
Terbutaline is secreted via breast milk, but effect on the infant is unlikely at therapeutic doses.

Effects on ability to drive and use machines
Terbutaline has no or negligible influence on the ability to drive and use machines.

Drug Interactions
Beta-blocking agents (including eye drops), especially the non-selective ones such as propranolol, may partially or totally inhibit the effect of beta-stimulants. Therefore, Terbutaline preparations and non-selective beta-blockers should not normally be administered concurrently. Terbutaline should be used with caution in patients receiving other sympathomimetics.

Halogenated anaesthetics
Halothane anaesthesia should be avoided during $beta_2$-agonists treatment, since it increases the risk of cardiac arrhythmias. Other halogenated anaesthetics should be used cautiously together with $beta_2$-agonists.

Potassium depleting agents and hypokalemia
Owing to the hypokalaemic effect of beta-agonists, concurrent administration with Terbutaline of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia. Hypokalaemia also predisposes to digoxin toxicity.

Paediatric population
Interaction studies have only been performed in adults.

DOSAGE AND ADMINISTRATION
Posology
When used as maintenance therapy the patient should also receive optimal anti-inflammatory therapy, e.g. inhaled corticosteroids, leukotriene receptor antagonists.

In most patients, the use of terbutaline sulfate, based on the doses below, given 2-4 times daily will be sufficient to relieve bronchospasm. In acute, severe asthma, additional doses may be necessary.

Multidose Bottles:
Adults: 0.5 to 1 ml (5 to 10mg) diluted to required nebulizer volume with sterile physiological saline.
Children: 0.2 to 0.5ml (2 to 5mg), see table, diluted to required nebulizer volume with sterile physiological saline.

Table below illustrating ml undiluted solution from multidose bottle required for administration to children.

Age	Average (kg)	Weight (lb)	Terbutaline (mg)	Undiluted Solution (ml)
<3	10	22	2.0	0.2
3	15	33	3.0	0.3
6	20	44	4.0	0.4
8+	25+	55+	5.0	0.5

Elderly: Dosage as for adults.

Method of administration
Instructions for use and cleaning are provided in the Patient Information Leaflet which can be found in each pack.

Private purchase of nebulizer devices for use at home to deliver rescue therapy for the acute treatment of asthma in children and adolescents is not recommended.

Only specialist in respiratory medicine should initiate and clinically manage use of nebulisers and associated nebulized medicines at home for acute treatment of asthma in children and adolescents.

Children should be trained in the correct use of their device to deliver rescue therapy and use should be supervised by a responsible adult.

Urgent medical assistance should be sought if worsening asthma symptoms are not relieved by rescue medicines, even if there is short-term recovery following use of prescribed medication.

OVERDOSAGE
i) Possible symptoms and signs:
Headache, anxiety, tremor, nausea, tonic cramp, palpitations, tachycardia and arrhythmia. A fall in blood pressure sometimes occurs. Laboratory findings: Hypokalaemia, hyperglycaemia and metabolic acidosis sometimes occur.

ii) Treatment:
Mild and moderate cases: Reduce the dose.

Severe cases: Gastric lavage, administration of activated charcoal (where suspected that significant amounts have been swallowed). Determination of acid-base balance, blood sugar and electrolytes, particularly serum potassium levels. Monitoring of heart rate and rhythm and blood pressure. Metabolic changes should be corrected. A cardio selective beta-blocker (e.g. metoprolol) is recommended for the treatment of arrhythmias causing haemodynamic deterioration. The beta-blocker should be used with care because of the possibility of inducing bronchoconstriction: use with caution in patients with a history of bronchospasm. If the $beta_2$-mediated reduction in peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

ROUTE OF ADMINISTRATION
Inhalation.

STORAGE CONDITIONS
Store below 30°C.
Protect from light.
Keep container tightly closed.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION
Bottle of 10 mL.

Date of revision: 10th October 2025

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
No. 11A, Jalan P/1, Kawasan Perusahaan Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

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