Bricanyl®
Terbutaline Sulfate

PRODUCT INFORMATION

NAME OF THE DRUG

BRICANYL® is Terbutaline Sulfate, 2-(tert-butylamino)-1-(3,5-dihydroxyphenyl) ethanol sulfate, a sympathomimetic bronchodilator with a degree of selective $\beta_2$-stimulant activity on the respiratory system.

DESCRIPTION

BRICANYL TURBUHALER® is a breath activated multiple dose powder inhaler free from propellant, lubricant, preservative, carrier substances or other additives.

*BRICANYL RESPULES® are a 5 mg in 2 mL nebulising solution with sodium chloride, disodium edetate, hydrochloric acid (for pH adjustment) and water for injections as inactive ingredients.

BRICANYL Elixir is a 0.3 mg/mL oral solution with sorbitol, glycerol, citric acid monohydrate, sodium hydroxide, sodium benzoate, disodium edetate, ethanol, purified water and raspberry flavour as inactive ingredients.

BRICANYL solution for injection contains 0.5 mg/mL of Terbutaline Sulfate with sodium chloride, hydrochloric acid (for pH adjustment) and water for injections as the inactive ingredients.

PHARMACOLOGY

The tertiary butyl group attached to the terminal nitrogen of the Terbutaline molecule is thought to confer selective stimulation of the pulmonary $\beta_2$-receptors and only relatively minor stimulation of cardiac $\beta_1$ receptors. The presence of the two phenolic hydroxyl groups in the meta positions confers resistance to metabolism by the enzyme catechol-o-methyl transferase. The potent bronchospasmolytic effect is rapid in onset and reaches a maximum about 30 minutes after subcutaneous injection, 1 hour after aerosol and 2 - 3 hours after oral administration. The duration of action is between 4 and 5 hours. In addition to its bronchospasmolytic effect, Terbutaline has also been shown to improve mucociliary clearance. Metabolism of Terbutaline Sulfate which is ingested orally or swallowed following inhalation is principally by conjugation in the gastrointestinal mucosa. The drug is absorbed unchanged from the respiratory tract and is excreted mainly as such in the urine. Practically all of an administered dose of Terbutaline is eliminated after 72 hours.
INDICATIONS

For relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma or in other situations known to induce bronchospasm.

BRICANYL TURBUHALER
BRICANYL TURBUHALER is intended for short-term management of bronchospasm as well as maintenance therapy.

BRICANYL Injection
BRICANYL injection solution is recommended for acute use only.

CONTRAINDICATIONS

Hypersensitivity to sympathomimetic amines or any other ingredient.

PRECAUTIONS

Cardiovascular diseases and hyperthyroidism
Caution is advised when Terbutaline is administered to patients with thyrotoxicosis and to patients with hypertension, coronary artery disease, arrhythmias and tachyarrhythmia.

Cardiovascular effects may be seen with sympathomimetic drugs, including BRICANYL. 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 BRICANYL, 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.

Arrhythmogenic potential
β₂-stimulants have an arrhythmogenic potential which must be considered for each patient when receiving treatment for bronchospasm.

Diabetes
Due to the blood-glucose increasing effects of β₂-stimulants, extra blood glucose controls are initially recommended when diabetic patients are commenced on Terbutaline.

Sensitivity to sympathomimetic amines
Some patients may be unusually sensitive to β-adrenergic stimulants. Terbutaline should be used with caution when an increased susceptibility to sympathomimetic amines can be expected for instance in other patients with hyperthyroidism not yet adequately controlled.
Nebulising solution/pulmonary conditions
Positive pressure delivery systems (IPPB) for respiratory drugs should not be used in pulmonary conditions involving pneumothorax, air cyst or mediastinal emphysema unless special drainage is carried out.

Lack of response
If the usual dose does not provide the usual relief, a non-responsive state may be developing. If a previously effective dose lasts less than usual, patients should be instructed to consult a doctor.

Hypokalaemia
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 (see Precautions - Interactions with other drugs). It is recommended that serum potassium levels are monitored in such situations.

Acute asthma
If patients with an acute attack of asthma fail to respond to a dry powder inhaler of $\beta_2$-agonist they should be advised to follow their personal asthma action plan. Failure to respond to $\beta_2$-agonists in general can be due to various reasons related to drug administration or the disease itself. Particularly in children 5 years or younger, and exceptionally in other cases, inspiratory flow through a dry powder inhaler may not be sufficient for optimal drug delivery. If a non-response occurs, medical help should be sought while a $\beta_2$-agonist treatment is continued. In such a situation, and if available, a nebuliser or pressurised metered dose inhaler with spacer should be used. (see also Precautions - Lack of response).

Cardionecrosis
Animal studies suggest that cardionecrotic lesions may occur with high doses of some sympathomimetic amines. On this evidence, it is not possible to exclude myocardial lesions as a possible hazard resulting from long-term treatment.

Use in pregnancy Category A
Although no adverse effects in pregnant women or their foetuses have been reported, care with BRICANLY, as with all other drugs, is recommended during the first 3 months of pregnancy.

Use in lactation
Although Terbutaline is secreted into breast milk, and milk concentrations are approximately those in maternal plasma, two individual case studies indicate that the infant is likely to receive 0.2 - 0.7% of the maternal dose (0.4 and 0.7 microgram / kg / day respectively), depending (for example) on the time of feeding in relation to administration of the drug. In the 4 infants studied this did not result in any signs of $\beta$-adrenoceptor stimulation.

Transient hypoglycaemia has been reported in newborn preterm infants after maternal $\beta_2$-agonist treatment.
Interactions with other drugs
Care is recommended if it is proposed to administer Terbutaline in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.

β-adrenergic blocking drugs, including eye drops, may inhibit the bronchodilating effect of sympathomimetic bronchodilators and may increase airways resistance in asthmatic patients.

Hypokalaemia may result from β2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics (see Precautions - Hypokalaemia).

ADVERSE REACTIONS

Most of the side effects are characteristic of sympathomimetic amines. The incidence and severity of particular side effects depends on the dose and rate of administration. An initial dose-titration will often reduce side effects. At recommended therapeutic doses, the frequency of side-effects is minimal.

More common reactions
More commonly observed side effects include tremor and headache. Commonly observed side effects include nervousness, tachycardia, palpitations, tonic muscle cramps and hypokalaemia.

Less common reactions

Cardiovascular   Ectopic beats
Gastrointestinal Nausea, vomiting, bad taste, diarrhoea
General          Sweating
Musculo-skeletal Muscle twitching, cramps
Nervous system   Drowsiness, dizziness, sleep disturbance, behavioural disturbances (such as agitation, hyperactivity, restlessness)
Dermatological  Rash, urticaria, exanthema

Serious or life-threatening reactions
Cardiac arrhythmias (eg atrial fibrillation, supraventricular tachycardia and extrasystoles) and myocardial ischaemia have been rarely reported.

Overdose of Terbutaline preparations may produce significant tachycardia, arrhythmia and hypotension (see Overdosage). In rare cases, through unknown mechanisms, drugs for inhalation may cause bronchospasm.
DOSAGE AND ADMINISTRATION

Inhaled bronchodilators should be used as required rather than regularly.

Dosage should be individualised. If long-term use of Terbutaline is proposed, particularly if the patient is asked to take Terbutaline in conjunction with other medications, objective pulmonary function testing (for example, by peak flow meter or spirometer) may be useful as part of assessment of the efficacy or treatment.

Adults and Children Over 12 Years

Oral:

BRICANYL Elixir (0.3 mg/mL Terbutaline)
10 to 15 mL up to 3 times daily.

Inhalational:

BRICANYL TURBUHALER (1 inhalation = 500 µg Terbutaline)
1 inhalation as required up to every 4 to 6 hours. In severe cases the single dose may be increased to 3 inhalations. The total daily dose should not exceed 12 inhalations per 24 hours.

*BRICANYL RESPULES (2.5 mg/mL):
May be delivered by any efficient nebulising device.
Dose: 2.5 to 5 mg (1 – 2 mL) as required up to every 6 hours. In severe cases, up to 4 mL may be nebulised.

The isotonic solution may be used undiluted or diluted with sterile normal saline according to individual requirements.

Any solution remaining in the RESPULE or nebulising device should be discarded after therapy.

Parenteral (0.5 mg/mL Terbutaline) subcutaneous:
0.5 mL. Repeat as required up to every 6 hours.

Paediatric

Oral:

BRICANYL Elixir (0.3 mg/mL Terbutaline).
0.075 mg (0.25 mL) /kg/dose. Repeat as required up to every 6 hours.

Inhalational:

BRICANYL TURBUHALER (1 inhalation = 500 µg Terbutaline)
1 inhalation as required up to every 4 to 6 hours. In severe cases the single dose may be increased to 2 inhalations. The total daily dose should not exceed 8 inhalations per 24 hours.
*BRICANYL RESPULES (2.5 mg/mL):*
May be delivered by any efficient nebulising device.
Dose: 0.2 mg/Kg/dose (0.08 mL/Kg/dose) repeated as required up to every 4 hours.

The isotonic solution may be used undiluted or diluted with sterile normal saline according to individual requirements.

Any solution remaining in the RESPULE or nebulising device should be discarded after therapy.

**Use in Children**
Dosage schedules for children for oral formulations of Terbutaline should be prescribed on a mg/kg basis. The larger safety margins with the dry powder formulation permit a less specific dosage schedule.

Oral administration is indicated in children who are unable to inhale satisfactorily via a metered dose inhaler and who do not have access to a compressor/nebuliser unit.

BRICANYL TURBUHALER is suitable for use by children since it is breath activated and does not require co-ordination of dose release and inhalation as with use of aerosol inhalers.

**Impaired hepatic function**
Hepatic failure has not been shown to influence the metabolism of Terbutaline. However, caution should be exercised in patients with impaired liver function.

**Impaired renal function**
As Terbutaline Sulfate is largely excreted in urine, caution should be exercised in patients with renal impairment.

**OVERDOSAGE**

**Possible symptoms and signs**
Too frequent administration, as with other sympathomimetic agents, may cause nausea, headaches, changes in blood pressure, anxiety, tension, restlessness, insomnia, tremor, excitement, tonic muscle cramps, palpitations, tachycardia and cardiac arrhythmias. The symptoms and signs are those characteristic of excessive sympathetic stimulation.

**Laboratory findings**
Hyperglycaemia and lactacidosis sometimes occur. β₂-agonists may cause hypokalemia as a result of redistribution of potassium.

**Treatment**
The specific antidote for accidental overdosage with Terbutaline Sulfate is a cardio-selective β-adrenergic blocking drug such as metoprolol (5 - 10mg by slow intravenous injection, repeated if necessary after 5 minutes). β-blockers should be used with care because of the possibility of inducing bronchospasm in sensitive individuals.
PRESENTATION

Bricanyl® Elixir (sugar-free)
0.3 mg/mL in bottles of 300 mL.

Bricanyl® Turbuhaler®
500 µg per inhalation, breath activated; propellant and additive free. 200 doses.

*Bricanyl® Respules®
5 mg in 2 mL solution in polyethylene unit dose containers. Packs of 30.

Bricanyl® Injection Solution
0.5 mg/mL of 5 x 1 mL ampoules.

POISON SCHEDULE OF THE DRUG

S3 - Pharmacist Only Medicine
BRICANYL TURBUHALER

S4 - Prescription Medicine
BRICANYL *RESPULES, elixir and injection

STORAGE

BRICANYL TURBUHALER
Store below 30°C. Replace cap firmly after use.

BRICANYL Elixir
Store below 30°C.

*BRICANYL RESPULES
Store below 30°C. BRICANYL RESPULES should be protected from light by keeping them in the foil envelopes. Unused, unopened RESPULES should be discarded 3 months after opening of the foil pack.

BRICANYL Injection
Store below 25°C. Protect from light.

Solutions containing Terbutaline are sensitive to excessive heat and light. Solutions should not be used if discoloured.
NAME AND ADDRESS OF THE SPONSOR

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*Denotes non-marketed product