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SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: TOCOLYSIS
Oral terbutaline sulfate has not been approved for and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for maintenance tocolysis in the outpatient or home setting.
During pregnancy, serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See *Contraindications, Tocolysis*.]

1 NAME OF THE MEDICINAL PRODUCTS

BRICALIN®
RESPIRATOR SOLUTION
TURBUHALER® (POWDER FOR INHALATION)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRICALIN RESPIRATOR SOLUTION:
Each ml contains: Terbutaline sulfate 10 mg

BRICALIN TURBUHALER
Terbutaline Sulphate 0.5mg/dose.

For excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Bricalin Respirator Solution: clear, colorless to faintly yellow solution.

Bricalin Turbuhaler: white to off white inhalation powder.
Breath-actuated metered dose powder inhaler.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of bronchospasm in patients with reversible obstructive airway disease including asthma, chronic bronchitis and emphysema.
Bricalin Respirator Solution is especially valuable for the relief of severe bronchospasm.

4.2 Posology and method of administration

BRICALIN RESPIRATOR SOLUTION

The usual dose of terbutaline by wet aerosol is 2-5 mg or up to 10 mg in severe cases.
Administration of Bricalin Respirator Solution can be via a nebulizer or an intermittent positive pressure breathing (IPPB) machine.
Bricalin Respirator Solution must be diluted with sterile physiological saline to ensure delivery of the correct dose. Such dilution will depend on two factors: the period of time over which the dose is to be delivered, and the design of the equipment used to deliver the solution (capacity, dead space, etc...).
Administration over a short period of time in a machine capable of completely utilizing small volumes of liquid (e.g. Bird Respirator) may indicate little, if any dilution (e.g. 3-5 ml).
Use of a nebulae such as Ventimask, Wright or De-Vilbiss, requires a dilution suited to the equipment and administration time. For such chronic administration, Bricalin Respirator Solution should be given at a rate of 1-2 mg per hour in a solution of 100 mcg/ml (1:100 dilution).
Once the bottle has been opened, the contents should be used within 3 months.

BRICALIN TURBUHALER

Note: Bricalin Turbuhaler should be stored with the cover tightened.

Bricalin Turbuhaler should be administered to children, only under adult supervision.
The usual dosage for adults and children is 1 inhalation repeated every 6 hours. Dosing should not be repeated more often than every 4 to 6 hours.
The use of Bricalin Turbuhaler can be continued as medically indicated to control recurring bouts of bronchospasm.

Notes for Bricalin Respirator Solution, Bricalin Turbuhaler

As initial therapy, inhaled bronchodilators should be used as required, rather than regularly.
If a previously effective dosage regimen no longer provides the same symptomatic relief, the patient should seek medical advice as soon as possible, since this could be a sign of worsening asthma. Repeated inhalations of β2-agonists must not delay reassessment of the asthma therapy.

4.3 Contraindications

Bricalin preparations are contraindicated in patients with a history of sensitivity to terbutaline sulphate or to any other ingredient of the preparations.

Tocolysis
Oral terbutaline sulfate is contraindicated for the treatment of acute or maintenance tocolysis. [See Boxed Warning: Tocolysis.]

4.4. Special warnings and special precautions for use

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

For Bricalin Turbuhaler only: With each inhalation a fraction of the delivered dose will be deposited in the oral cavity. To minimize unnecessary systemic exposure to terbutaline, the patients should be advised to, when possible, rinse their mouth after each use.

If a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should urgently seek further medical advice. 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.

As for all beta$_2$-agonists caution should be observed in patients with thyrotoxicosis.

Due to the positive inotropic effect of 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 Bricalin 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 hyperglycemic effects of beta$_2$-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalemia 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 section 4.5, Interactions). It is recommended that serum potassium levels are monitored in such situations.

<u>For Bricalin Respirator Solution only</u>
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 (see Section 4.8 Undesirable effects & 4.9 Overdose). In patients not adequately responding to acute Bricalin therapy, consideration should be given to the presence of lactic acidosis as a possible contributing factor to ongoing respiratory symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

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, Bricalin preparations and non-selective beta-blockers should not normally be administered concurrently. Bricalin should be used with caution in patients receiving other sympathomimetics.

Hypokalemia may result from beta$_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics (*see Section 4.4, Special Warnings and Precautions for use*).

4.6 Pregnancy and lactation

There are, no adequate and well-controlled studies of terbutaline sulfate in pregnant women. Published animal studies show that rat offspring exhibit alterations in behavior and brain development, including decreased cellular proliferation and differentiation when dams were treated subcutaneously with terbutaline during the late stage of pregnancy and lactation period. Terbutaline exposures in rat dams were approximately 6.5 times the common human dose in adults of 15 mg/day, on a mg/m^2 basis.

Oral terbutaline sulfate has not been approved for and should not be used for acute or maintenance tocolysis. In particular, terbutaline sulfate should not be used for tocolysis in the outpatient or home setting. Serious adverse reactions, including death, have been reported after administration of terbutaline sulfate to pregnant women. In the mother, these adverse reactions include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration. [See Boxed Warning: Tocolysis and Contraindications, Tocolysis.]

In animal embryofetal developmental studies, no teratogenic effects were observed in offspring when pregnant rats and rabbits received terbutaline sulfate at oral doses up to 50 mg/kg/day, approximately 32 and 65 times, respectively, the maximum recommended daily oral dose for adults, on a mg/m^2 basis.
Terbutaline sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Terbutaline is secreted via breast milk but any effect on the infant is unlikely at therapeutic doses.
Transient hypoglycemia has been reported in newborn preterm infants after maternal $beta_2$-agonist treatment.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

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.

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

Frequency Classification	**Adverse Drug Reaction**	
	System Organ Class (SOC)	**Preferred term (PT)**
Very Common (>1/10)	Nervous System Disorders	Tremor Headache
Common (>1/100, <1/10)	Cardiac Disorders	Tachycardia Palpitations
	Musculoskeletal and Connective Tissue Disorders #	Muscle spasms
	Metabolism and Nutrition Disorders	Hypokalaemia (See section 4.4)
Not Known ^	Cardiac Disorders	Arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles Myocardial ischaemia (See section 4.4)
	Vascular Disorders	Peripheral vasodilation
	Immune System Disorders	Hypersensitivity reactions including angioedema, bronchospasm, hypotension and collapse
	Gastrointestinal Disorders	Nausea Mouth and throat irritation
	Psychiatric Disorders	Sleep disorder and Behavioural disturbances, such as agitation and restlessness
	Metabolism and Nutritional Disorders	Lactic acidosis [1]
	Respiratory, Thoracic and Mediastinal Disorders	Paradoxical bronchospasm *
	Skin and Subcutaneous Tissue Disorders	Urticaria Rash

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. Bricalin therapy should be discontinued and after assessment, an alternative therapy initiated.

[1] For Bricalin Respirator Solution only

4.9 Overdose

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 (see Section 4.4. Special warnings and special precautions for use).

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 cardioselective 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: selective $beta_2$-agonist, terbutaline,
ATC code: R03A C03.

Terbutaline is a selective beta2-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.

5.2 Pharmacokinetic properties

Basic parameters have been 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 $t_{½}$ 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 sulphate conjugate and also some glucoronide conjugate can be found in the urine.

5.3 Preclinical safety data

The major toxic effect of terbutaline, observed in toxicological studies in rats and dogs at exposures in excess of maximum human exposure, is focal myocardial necrosis. This type of cardiotoxicity is a well known pharmacological manifestation seen after the administration of high doses of $beta_2$-agonists.

In rats, an increase in the incidence of benign uterine leiomyomas has been observed. This effect is looked upon as a class-effect observed in rodents after long term exposure to high doses of $beta_2$-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BRICALIN RESPIRATOR SOLUTION:

Sodium chloride, chlorobutanol hemihydrate, edetate disodium, hydrochloric acid (QS for pH adjustment), water for injection.

Sodium content: 2.3 mg per 1 ml

BRICALIN TURBUHALER
None.

6.2 Incompatibilities
None known.

6.3 Special precautions for storage
Bricalin Respirator Solution: Store in a dark place below 25°C.
Bricalin Turbuhaler: Store below 30ºC.

6.4 PRESENTATION
Bricalin Respirator Solution: bottle amber glass containing 15 ml.
Bricalin Turbuhaler: 100 doses Turbuhaler.

7 REGISTRATION NUMBERS:
Bricalin Respirator Solution: 034 89 22647 00.
Bricalin Turbuhaler: 054 27 26354 05; 054 27 26354 06.

8 MANUFACTURER
Teva Pharmaceutical Industries Ltd.
P.O. Box 3190, Petach Tikva 49131, Israel.

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