IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0970/036/004
Case No: 2055163

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Bricanyl Respules 5 mg/2 ml nebuliser solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/08/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bricanyl Respules 5 mg/ 2 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Terbutaline sulphate 2.5 mg/ml.
Each single dose Respule contains 2 ml (5 mg).

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution
A clear, aqueous, isotonic solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Terbutaline is a selective beta$_2$-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.

4.2 Posology and method of administration

In most patients, the use of terbutaline sulphate, 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.

Bricanyl Respules:

Adults:	1 or 2 Respules (5 or 10mg).
Children:	(>25kg) 1 Respule (5mg).
Children:	(<25kg) use multidose bottles.

The pH of Bricanyl Respules is 3 - 4.5.

Multidose Bottles:

Adults: 0.5 to 1 ml (5 to 10mg) diluted to required nebuliser volume with sterile physiological saline.

Children: 0.2 to 0.5ml (2 to 5mg), see table, diluted to required nebuliser volume with sterile physiological saline.

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

Age	Average Weight		mg Terbutaline	ml undiluted solution
	kg	lb		
<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.

4.3 Contraindications

Bricanyl preparations are contra-indicated in patients with a history of hypersensitivity to any of their constituents.

4.4 Special warnings and precautions for use

The patient's inhalation technique should be checked regularly, and the optimal dose of Bricanyl should be adjusted for each nebuliser.

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.

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.

Due to the positive inotropic effect of the $beta_2$-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Due to the hyperglycaemic effects of $beta_2$-stimulants, additional blood glucose measurements are initially recommended when Bricanyl therapy is commenced in diabetic patients.

Potentially serious hypokalaemia may result from $beta_2$-agonist therapy, mainly with parenteral or nebulised administration. Particular caution is advised in acute severe asthma, as this effect may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and/or diuretics. It is recommended that serum potassium levels are monitored in such situations

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

Hypokalaemia 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

Although no teratogenic effects have been observed in animals or in patients, Bricanyl should only be administered with caution during the first trimester of pregnancy.

Terbutaline is secreted via breast milk, but any effect on the infant is unlikely at therapeutic doses.

Transient hypoglycaemia has been reported in newborn preterm infants after maternal beta$_2$-agonist treatment.

4.7 Effects on ability to drive and use machines

Bricanyl does not affect the ability to drive or use machines.

4.8 Undesirable effects

The frequency of adverse reactions is low at the recommended dose. Terbutaline given by inhalation is unlikely to product 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.

Frequency Classification	Adverse Drug Reaction	
	System Organ Class (SOC)	Preferred term (PT)
Very Common (≥1/10)	Nervous System Disorders	Tremor Headache
Common (<1/10 and ≥ 1/100)	Cardiac Disorders	Tachycardia Palpitations
	Musculoskeletal and Connective Tissue Disorders	Muscle spasms
	Metabolism and Nutrition Disorders	Hypokalaemia
Unknown*	Cardiac Disorders	Arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles Myocardial ischaemia
	Gastrointestinal Disorders	Nausea
	Psychiatric Disorders	Sleep disorder and Behavioural disturbances, such as agitation and restlessness
	Nervous System Disorders	Psychomotor hyperactivity
	Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm**

	Skin and Subcutaneous Tissue Disorders	Urticaria Rash

* Reported spontaneously in post-marketing data and therefore frequency regarded as unknown
Preterm labour
** Drugs for inhalation may through unspecified mechanisms cause bronchospasm.

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.

ii) Treatment:

Mild and moderate cases: Reduce the dose.

Severe cases: Gastric lavage: 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-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 $beta_2$-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.

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, is focal myocardial necrosis. This type of cardiotoxicity is a well-known class-effect, and the effect of terbutaline is similar to or less pronounced than that of other beta-receptor agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium edetate
Hydrochloric acid
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Unopened: 3 years
The preparation is stable for 24 hours in the reservoir of the nebuliser.
Single does units in an opened foil envelope should be used within 3 months.

6.4 Special precautions for storage

Do not store above 30°C. Keep respules in the outer foil envelope.

6.5 Nature and contents of container

Single dose, plastic units (Respules) in cartons of 20 Respules, as 4 strips of 5 units, each wrapped in a foil envelope.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Bricanyl Respules will not normally require dilution at recommended doses.
If dilution is required use sterile normal saline.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd.
600 Capability Green
Luton
LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 970/36/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st September 1982

Date of last renewal: 1st September 2007

10 DATE OF REVISION OF THE TEXT

August 2009