Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bricanyl 500 micrograms/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 500 micrograms Terbutaline sulfate.

Excipient(s) with known effect: 1 ml also contains sodium (<1 mmol/ml), as sodium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion
A clear aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bronchodilation
Terbutaline is a selective beta$_2$-adrenergic agonist recommended for the relief of bronchospasm in bronchial asthma and other bronchopulmonary disorders in which bronchospasm is a complicating factor.

For the short term management of uncomplicated premature labour
To arrest labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.

4.2 Posology and method of administration

Posology
The dosage should be individualised.

For bronchodilation
When a rapid therapeutic response is required, Bricanyl can be administered by any of the three standard parenteral routes: subcutaneous, intramuscular, or i.v. bolus. The preferred routes will usually be subcutaneous or intramuscular. When given as an i.v. bolus the injection must be made slowly noting patient response.

Adults
0.5 -1 ml (0.25 - 0.5 mg) up to four times a day.

Paediatric population
2 -15 years: 0.01 mg/kg body weight to a maximum of 0.3 mg total.

Age	Average weight		mg	ml
	kg	(lb)	terbutaline	volume
<3	10	(22)	0.1	0.2
3	15	(33)	0.15	0.3
6	20	(44)	0.2	0.4
8	25	(55)	0.25	0.5
10+	30+	(66+)	0.3	0.6

By infusion
3 - 5 ml (1.5 - 2.5 mg) in 500 ml 5% dextrose, saline or dextrose/saline given by continuous intravenous infusion at a rate of 10 - 20 drops (0.5 - 1 ml) per minute for 8 to 10 hours. A corresponding reduction in dosage should be made for children.

Elderly: Dosage as for adults.

In the short term management of uncomplicated premature labour
Treatment with Bricanyl should only be initiated by obstetricians/physicians experienced in the use of tocolytic agents. It should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetus health status.

Duration of treatment should not exceed 48 hours as data show that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours; no statistically significant effect on perinatal mortality or morbidity has been observed in randomised, controlled trials. This short term delay may be used to implement other measures known to improve perinatal health.

Bricanyl should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications to the use of terbutaline (see section 4.3). This should include an adequate assessment of the patient's cardiovascular status with supervision of cardiorespiratory function and ECG monitoring throughout treatment (see section 4.4).

Initially 5 mcg/min should be infused during the first 20 minutes increasing by 2.5 mcg/min at 20 minute intervals until the contractions stop. More than 10 mcg /min should seldom be given, 20 mcg/min should not be exceeded.

The infusion should be stopped if labour progresses despite treatment at the maximum dose.

If successful, the infusion should continue for 1 hour at the chosen rate and then be decreased by 2.5 mcg/min every 20 minutes to the lowest dose that produces suppression of contractions.

Special cautions for infusion: The dose must be individually titrated with reference to suppression of contractions, increase in pulse rate and changes in blood pressure, which are limiting factors. These parameters should be carefully monitored during treatment. A maximum maternal heart rate of 120 beats per min should not be exceeded.

Careful control of the level of hydration is essential to avoid the risk of maternal pulmonary oedema (see section 4.4). The volume of fluid in which the drug is administered should thus be kept to a minimum. A controlled infusion device should be used, preferably a syringe pump.

Dilution:

The recommended infusion fluid is 5% dextrose.

If a syringe pump is available, the concentration of the drug infused should be 0.1 mg/ml (10 ml Bricanyl Injection should be added to 40 ml of 5% dextrose).

At this dilution:
5 mcg/min ≡0.05 ml/min
10 mcg/min ≡ 0.1 ml/min

If no syringe pump is available, the concentration of the drug should be 0.01 mg/ml (10 ml Bricanyl Injection should be added to 490 ml of 5% dextrose).

At this dilution:
5 mcg/min ≡ 0.5 ml/min
10 mcg/min ≡ 1 ml/min.

Saline should be avoided during pregnancy since the use of this diluent may increase the risk of producing pulmonary oedema. If saline has to be used, the patients should be carefully monitored.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In the treatment of premature labour Bricanyl is contra-indicated in the following conditions:

- A gestational age of < 22 weeks.
- As a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- Threatened abortion during the 1st and 2nd trimester.
- Any conditions of the mother or foetus in which prolongation of the pregnancy is hazardous e.g. severe toxaemia, intra-uterine infection, vaginal bleeding resulting from placenta praevia, eclampsia orsevere pre eclampsia, placental abruption, or cord compression.
- Intrauterine foetal death, known lethal congenital or lethal chromosomal malformation.
- Bricanyl is also contraindicated in any pre-existing medical conditions with which a betamimetic would have an untoward effect e.g., pulmonary hypertension and cardiac disorders such as hypertrophic obstructive cardiomyopathy or any type of obstruction of the left ventricular outflow tract, e.g. aortic stenosis.

4.4 Special warnings and precautions for use

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 postmarketing data and published literature of myocardial ischaemia associated with beta agonists.

Due to the positive inotropic effect of the beta$_2$-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Bronchospasm

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.

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 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 hypokalemic effect may be potentiated by concomitant treatments (see section 4.5). 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 (see section 4.8). In patients not adequately responding to acute Bricanyl therapy, consideration should be given to the presence of lactic acidosis as a possible contributing factor to ongoing respiratory symptoms.

Tocolysis

Any decision to initiate therapy with Bricanyl should be undertaken after careful consideration of the risks and benefits of treatment.

Treatment should only be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetal health status. Tocolysis with beta-agonists is not recommended when membranes have ruptured or the cervix dilation is beyond 4cm.

Bricanyl should be used with caution in *tocolysis* and supervision of cardiorespiratory function, and ECG monitoring, should be performed throughout treatment.

The following monitoring measures must be constantly applied to the mother and, when feasible/appropriate, to the foetus:

- Blood pressure and heart rate.
- ECG.
- Electrolyte and fluid balance – to monitor for pulmonary oedema.
- Glucose and lactate levels – with particular regard to diabetic patients-during treatment of preterm labour, when high doses of Bricanyl are used, diabetic mothers may develop hyperglycaemia and lactacidosis. In these patients glucose and acid-base balance should be carefully monitored.
- Potassium levels– beta-agonists are associated with a decrease in serum potassium which increases the risk of arrhythmias (see section 4.5).

Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop.

Bricanyl should not be used as a tocolytic agent in patients with significant risk factors for, or a suspicion of any kind of pre-existing heart disease (e.g. tachyarrhythmias, heart failure, or valvular heart disease; see section 4.3*).* In premature labour, in a patient with known or suspected cardiac disease, a physician experienced in cardiology should assess the suitability of treatment before intravenous infusion with Bricanyl solution for injection.

An increased tendency to bleeding has been described in connection with caesarean section. In such a case you may give propranolol, 1- 2 mg i.v. to patients treated with Bricanyl solution for injection for preterm labour.

Pulmonary oedema

As maternal pulmonary oedema and myocardial ischaemia have been reported during or following treatment of premature labour with beta-agonists, careful attention should be given to fluid balance and cardio-respiratory function. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary oedema. Administration with a syringe pump as opposed to i.v. infusion will limit risk of fluid overload. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered (see section 4.2 and 4.8).

Blood pressure and heart rate

Increases in maternal heart rate of the order of 20 to 50 beats per minute usually accompany infusion of beta-agonists. The maternal pulse rate should be monitored and the need to control such increases by dose reduction or drug withdrawal should be evaluated on a case by case basis. Generally maternal pulse rate should not be allowed to exceed a steady rate of 120 beats per minute.

Maternal blood pressure may fall slightly during the infusion; the effect being greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 10 to 20 mmHg. The effect of infusion on foetal heart rate is less marked, but increases of up to 20 beats per minute may occur.

In order to minimise the risk of hypotension associated with tocolytic therapy, special care should be taken to avoid caval compression by keeping the patient in the left or right lateral positions throughout the infusion.

Diabetes

Administration of beta agonists is associated with a rise of blood glucose. Therefore blood glucose and lactate levels should be monitored in mothers with diabetes and diabetic treatment adjusted accordingly to meet the needs of the diabetic mother during tocolysis (see section 4.5).

Hyperthyroidism

Bricanyl should only be administered cautiously to patients suffering from thyrotoxicosis after careful evaluation of the benefits and risks of treatment.

Bricanyl contains Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule (1 ml), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of 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 Bricanyl preparations and non-selective beta-blockers should not normally be administered concurrently. Bricanyl should be used with caution in patients receiving other sympathomimetics.

Halogenated anaesthetics

Owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity, have been reported on interaction with halogenated anaesthetics. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with 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 $beta_2$-agonist.

Corticosteroids

Systemic corticosteroids are frequently given during premature labour to enhance foetal lung development. There have been reports of pulmonary oedema in women concomitantly administered with beta-agonists and corticosteroids.

Corticosteroids are known to increase blood glucose and can deplete serum potassium, therefore concomitant administration should be undertaken with caution with continuous patient monitoring owing to the increased risk of hyperglycaemia and hypokalaemia (see section 4.4).

Anti-diabetics

The administration of beta-agonists is associated with a rise of blood glucose, which can be interpreted as an attenuation of anti-diabetic therapy; therefore individual anti-diabetic therapy may need to be adjusted (see section 4.4).

Potassium depleting agents

Owing to the hypokalaemic effect of beta-agonists, concurrent administration of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, digoxin, 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 (see section 4.4).

There are some data which indicate that there is a risk of interaction between monoamine oxidase inhibitors, tricyclic antidepressants and terbuatline.

4.6 Fertility, pregnancy and lactation

Bronchospasm

Pregnancy

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.

Breast-feeding

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

Transient hypoglycaemia has been reported in newborn preterm infants after maternal β2-agonist treatment.

Premature Labour

Bricanyl is contraindicated for the treatment of premature labour before the gestational age of week 22 (see section 4.3).

4.7 Effects on ability to drive and use machines

Bricanyl Injection has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The intensity of the adverse reactions depends on dosage and route of administration. An initial dose titration will often reduce the adverse reactions. 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.

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).

Bronchial asthma. Chronic bronchitis, emphysema and other lung diseases where bronchospasm is a complicating factor.

Adverse Drug Reaction	**Frequency Classification**	
System Organ Class (SOC)		**Preferred term (PT)**
Metabolism and Nutritional Disorders	Common	Hypokalaemia
	Rare	Lactic Acidosis
Psychiatric Disorders	Not known*	Sleep disorder and Behavioural disturbances, such as agitation and restlessness
Nervous System Disorders	Very Common	Tremor Headache
	Not known*	Psychomotor hyperactivity
Cardiac Disorders	Common	Tachycardia Palpitations
	Not known *	Arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles Myocardial ischaemia
Gastrointestinal Disorders	Not known*	Nausea
Skin and Subcutaneous Tissue Disorders	Not known *	Urticaria

		Rash
Musculoskeletal and Connective Tissue Disorders	Common	Muscle spasms

* Reported spontaneously in post-marketing data and therefore frequency regarded as not known

Preterm labour

The most common undesirable effects of Bricanyl are correlated with the betamimetic pharmacological activity and may be limited or avoided by a close monitoring of haemodynamic parameters, such as blood pressure and heart rate, and an appropriate adjustment of the dose. They normally recede upon therapy discontinuation.

Adverse Drug Reaction	**Frequency Classification**	
System Organ Class (SOC)		**Preferred term (PT)**
Blood and Lymphatic System Disorders	Not known*	An increased tendency to bleeding in connection with caesarean section
Metabolism and Nutritional Disorders	Common	Hypokalaemia°
	Rare	Hyperglycaemia°
	Rare	Lactic acidosis
Psychiatric Disorders	Not known*	Sleep disorder and Behavioural disturbances, such as agitation and restlessness Hyperactivity
Nervous System Disorders	Very Common	Tremor Headache
Cardiac Disorders	Very Common	Tachycardia°
	Common	Palpitations° Decrease in diastolic pressure°
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles° Myocardial ischaemia (see section 4.4)°
Vascular Disorder	Common	Hypotension (see section 4.4)°
	Rare	Peripheral vasodilatation°
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Pulmonary oedema°
Gastrointestinal Disorders	Very Common	Nausea
Skin and Subcutaneous Tissue Disorders	Not know *	Urticaria Rash
Musculoskeletal and Connective Tissue Disorders	Not known*	Muscle spasms

* Reported spontaneously in post-marketing data and therefore frequency regarded as unknown

°These reactions have been reported in association with the use of short acting beta-agonists in obstetric indications and are considered class effects (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms: Headache, anxiety, tremor, nausea, tonic cramps, palpitations, tachycardia and arrhythmia. A fall in blood pressure sometimes occurs. Laboratory findings: hypokalaemia, hyperglycaemia and lactic acidosis sometimes occurs (see section 4.4).

Management

a) Mild and moderate cases: Reduce the dose.

b) Severe cases: 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.

c) In preterm labour: Pulmonary oedema: discontinue administration of Bricanyl.

A normal dose of loop diuretic (e.g. frusemide) should be given intravenously.

Increased bleeding in connection with Caesarean section: propranolol, 1 - 2 mg intravenously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: selective $beta_2$-adrenoreceptor agonist, terbutaline, ATC code: R03C 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 CNS: Low penetration into the blood-brain barrier at therapeutic doses, due to the highly hydrophilic nature of the molecule.

v) In the CVS: Administration of terbutaline results in cardiovascular effects mediated through β2-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 of distribution (VSS) - 114 L
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 sulfate conjugate and also some glucuronide 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
Hydrochloric acid (for pH-adjustment)
Water for injection

6.2 Incompatibilities

Bricanyl solution for injection should not be mixed with alkaline solutions, i.e. solutions with a pH higher than 7.0.

6.3 Shelf life

2 years.

Once opened and if further diluted, use immediately.

6.4 Special precautions for storage

Do not store above 25 ºC.

Keep ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear, Ph. Eur. Type I glass ampoule.
Packs of 5 x 1ml glass ampoule.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused content.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Bronchodilation: the recommended diluent is 5 % dextrose, saline or dextrose/saline.

In the management of premature labour the recommended infusion fluid is 5 % dextrose.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

8 MARKETING AUTHORISATION NUMBER

PA1019/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 07 January 2009

10 DATE OF REVISION OF THE TEXT

November 2020