SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bricanyl 0.3 mg/ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Terbutaline sulfate 0.3mg/ml.

Excipient(s) with known effect Each 1ml of Bricanyl Syrup contains 150 mg of Sorbitol and 2 mg of Ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution
Bricanyl syrup is a clear colourless raspberry flavoured oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Bricanyl Syrup has a duration of action of 7 to 8 hours. The minimum recommended dosage interval is therefore 7 hours.

Adults:	The starting dose should be 2 x 5ml spoonfuls 3 times in 24 hours. The dose may then be increased to 3 x 5ml spoonfuls 3 times in 24 hours if necessary to achieve adequate bronchodilation.
Elderly:	Dosage as for Adults.
Paediatric population:	The following dosage is recommended - 0.075mg (0.25ml)/kg body weight 3 times in a 24 hour period. Not more than 15 ml 3 times in 24 hours.

Method of administration
For oral use.

4.3 Contraindications

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

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 post-marketing data and published literature of myocardial ischaemia associated with beta agonists.

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

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 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.

Patients with persistent asthma who require maintenance therapy with beta$_2$-agonists should also receive optimal anti-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 Bricanyl 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 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.

Ethanol content
This medicinal product contains 2 mg of alcohol (ethanol) in each 1 ml. The amount in 45 ml of this medicinal product is equivalent to 3 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Sorbitol content
This medicinal product contains 105 mg sorbitol in each 1 ml. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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.

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 hypokalaemia

Owing to the hypokalaemic effect of beta-agonists, concurrent administration with Bricanyl 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 (see section 4.4). Hypokalaemia also predisposes to digoxin toxicity.

4.6 Fertility, pregnancy and lactation

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.

Maintenance treatment with oral $beta_2$-agonists for asthma and other pulmonary diseases should be used with caution at the end of pregnancy because of the potential tocolytic effect.

Breast-feeding
Terbutaline is secreted in breast milk, but 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 Syrup has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile.
The intensity of the adverse reactions depends on dosage and route of administration. 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 reactions.

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 Nutrition Disorders	Common	Hypokalaemia (See section 4.4)
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 (See section 4.4)
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. Bricanyl therapy should be discontinued and after assessment, an alternative therapy initiated.

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 the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Headache, anxiety, tremor, nausea, tonic cramp, palpitations, tachycardia, arrhythmia. A fall in blood pressure sometimes occurs.

Laboratory findings; hypokalaemia, hyperglycaemia and lactic acidosis sometimes occur.

Management
Mild and moderate cases: Reduce the dose.

Severe cases: Gastric lavage, administration of activated charcoal. Determination of acid-base balance, blood sugar and electrolytes, particularly serum potassium levels. Monitoring of the 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 the 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 β_2-agonist, terbutaline ATC code: R03C C03.

Terbutaline is a selective β_2 -adrenergic stimulant having the following pharmacological effects:-

i) *In the lung*: bronchodilation increased 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 result in cardiovascular effects mediated through β_2 -receptors in the peripheral arteries and in the heart e.g. in healthy subjects, 0.25 - 0.5mg 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.

<u>i.v. single dose</u>

Volume 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)

<u>Oral dose</u>

renal clearance (CLR):	1.925/ml/min (males)
renal clearance (CLR):	2.32ml/min (females)

The plasma concentration/time curve after iv 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)

<u>Bioavailability</u>
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.

5.3. Pre-clinical 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 β_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 exposure to high doses of β_2-agonists.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid
Disodium edetate
Ethanol
Glycerol
Sodium hydroxide
Sorbitol
Sodium benzoate
Essence of raspberry
Water

6.2 Incompatibilities

Not applicable.

6.3. Shelf Life

4 years.

6.4. Special Precautions for Storage

Do not store above 25ºC.

6.5 Nature and contents of container

Bottles of 100ml, 300ml and 1 litre.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
1 Francis Crick Avenue,
Cambridge,
CB2 0AA,
UK.

8. MARKETING AUTHORISATION NUMBER(S)

PL17901/0111

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th May 2002
Date of latest renewal: 12th May 2007

10 DATE OF REVISION OF THE TEXT

09/11/2022