Proposed packaging material		
Code	BRICASMA RESPULES 2.5 mg/ml-PI-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-131610-159730	
Code of previous version	N/A	
Changes	Risk of SABA Monotherapy	
Reference	☒CDS version: 4.0 (Doc ID-001555405) ☐CPIL version:	☐SmPC country/version/date: ☐GRL approval:
Name & Date	FR (24 November 2022)	

Bricasma® 2.5 mg/mL

terbutaline sulphate

Solution for nebulization

Qualitative and quantitative composition

1 ml contains terbutaline sulfate 2.5 mg.

Pharmaceutical form

Sterile solution for nebulization in single dose units of 2 ml.
BRICASMA solution for nebulization is isotonic and contains no preservatives.

Therapeutic indication

For the release of bronchospasm in chronic bronchitis, emphysema and other lung diseases where bronchospasm is a complicating factor.

Posology and method of administration

Inhaled bronchodilators should, as initial therapy, be used as required rather than regularly.

BRICASMA solution for nebulization is to be used in nebulizers with or without assisted breathing in acute or subacute disorders where conventional inhalers prove unsatisfactory and in maintenance therapy in severe broncho-obstructive conditions.

Dosage should be individual.
Body weight > 25 kg: 5 mg (1 single dose unit, 2 ml) is inhaled 2 up to 4 times in a 24 h period.

Contraindication

Hypersensitivity to any of the ingredients.

Special warnings and special precautions for use

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

Irrespective of asthma severity, having uncontrolled asthma is an important risk factor for exacerbations. Excessive regular use of short-acting ß$_2$-agonists (SABA) is associated with an increased risk of severe exacerbations and mortality.

In mild asthma patients, there is an increased risk of severe exacerbations associated with over-reliance on SABA monotherapy.

Patients who are prescribed regular anti-inflammatory therapy should be advised to continue taking their anti-inflammatory medication even when symptoms decreases and they do not require BRICASMA

BRICASMA should be used with caution when an increased susceptibility to sympathomimetic amines can be expected for instance in patients with hyperthyroidism not yet under adequate control.

If a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should seek medical care as soon as possible as this could be sign of worsening asthma and repeated inhalations of ß$_2$-agonists must then not delay reassessment of the asthma therapy.

As for all β_2-agonists caution should be observed in patients with thyrotoxicosis. Cardiovascular effects may be seen with sympathomimetic drugs, including BRICASMA. There is some evidence from post-marketing data and published literature 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 BRICASMA 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 β_2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Due to the positive inotropic effect of ß$_2$-agonists, this drug should not be used with hypertrophic cardiomyopathia.

However these drugs have an arrhythmogenic potential which must be considered in the treatment the individual lung patient.

Terbutaline is not indicated and should not be used for the management of preterm labor. Serious adverse reactions have been reported following administration of terbutaline sulfate to women in labor.

These reports have included transient hypokalemia, pulmonary edema (sometimes after delivery), and hypoglycemia in the mother and / or neonatal child. Maternal death has been reported with terbutaline sulfate and other drugs of this class.

There have been rare reports of seizures occurring in patients receiving terbutaline, which do not recur when the drug is discontinued and have not been explained on any other basis.

Terbutaline sulfate is a sympathomimetic amine and such should be used with caution in patients with cardiovascular disorders (including arrythmias, coronary insufficiency and hypertension), in patients with hyperthyroidism or diabetes mellitus, history of seizures, or in patients who are unusually responsive to sympathomimetic amines.

Potentially serious hypokalaemia may result from β_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 *Interactions with other medicinal products and other forms of interaction)*. It is recommended that serum potassium levels are monitored in such situations. Patients susceptible to hypokalemia should be monitored because transient early alls in serum potassium levels have been reported with ß$_2$-agonist.

Immediate hypersensitivity reactions and exacerbation of bronchospasm have been reported after terbutaline administration.

Safety and effectiveness in children below the age of 12 have not been established.

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 Undesirable *effects* and *Overdose*). In patients not adequately responding to acute Bricasma therapy, consideration should be given to the presence of lactic acidosis as a possible contributing factor to ongoing respiratory symptoms.

Interactions with other medicinal products and other forms of interaction

ß-receptor blocking agents (including eye-drops), especially those, which are non-selective, may partly or totally inhibit the effect of ß-receptor stimulant.

Halogenated anaesthetics

Halothane anaesthesia should be avoided during β2-agonists treatment, since it increases the risk of cardiac arrhythmias. Other halogenated anaesthetics should be used cautiously together with β2-agonists.

Potassium depleting agents and hypokalaemia

Owing to the hypokalaemic effect of beta-agonist, concurrent administration with BRICASMA of serum potassium depleting agents know to be 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 arrythmias arising as a result of hypokalaemia (see Special warnings and special precautions for use). Hypokalaemia also predisposes to digoxin toxicity.

Pregnancy and lactation

No teratogenic effects have been observed in patients or in animals. However, caution is recommended during the first trimester of pregnancy.

Terbutaline passes over to breast milk but an influence on the child is unlikely with therapeutic doses.

Transient hypoglycemia has been reported in newborn preterm infants after maternal β_2-agonist treatment.

Effects on ability to drive and use machines
BRICASMA does not affect the ability to drive or use machine.

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.

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	Tonic muscle cramps
	Metabolism and nutrition disorders	Hypokalaemia
Rare <1/1000 and ≥1/10000, Frequency unknown*	Cardiac disorders	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles myocardial ischemia
	Gastrointestinal disorders	Nausea
	Psychiatric disorders	Sleep disturbances and behavioural disturbances, such as agitation, hyperactivity and restlessness
	Metabolism and nutritional disorders	Lactic acidosis
	Skin and subcutaneous tissue disorders	Urticaria and exanthema

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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:

Pusat Farmakovigilans: Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia
Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21- 4244691 Ext. 1079
Website: http://e-meso.pom.go.id/

Overdose

Too frequent administration, as with other sympathomimetic agents, may cause nausea, headaches, changes in blood pressure, anxiety, tension, insomnia, tremor. The symptoms and sign are those characteristic of excessive sympathetic stimulation.

Possible symptoms and sign: Headache, anxiety, tremor, nausea, tonic muscle cramps, palpitation, tachycardia and cardiac arrhythmia. A fall in blood pressure sometimes occurs.

Laboratory findings: Hyperglycemia and lactacidosis sometimes occur (see *Special warnings and special precautions for use*). ß$_2$-agonist may cause hypokalemia as a result of redistribution of potassium.

Treatment of overdose: Usually no treatment is required.
If it can be suspected that significant amounts of terbutaline sulphate have been swallowed, the following measures should be considered:
Gastric lavage, activated charcoal. Determine of acid-base balance, blood sugar and electrolytes. Monitor of heart rate and rhythm and blood pressure. Metabolic changes should be corrected. A cardio-selective ß-blocker (e.g. metoprolol) is recommended for the treatment of arrhythmias causing a hemodynamic deterioration. The ß-blocker should be used with care because of the possibility of inducing bronchial obstruction.

If the ß$_2$-mediated reduction in peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

Mild and moderate cases: Reduce the dose. Then increase the dose more slowly until the broncholytic effect is insufficient.

Pharmacodynamic properties

Pharmacotherapeutic group: selective β_2-agonist, terbutaline, ATC code: R03A C03.

Terbutaline is an adrenergic agonist which predominantly stimulates ß$_2$ –receptors, thus producing relaxation of bronchial smooth muscle inhibition of the release of endogenous

spasmogens, inhibition of edema caused by endogenous mediators and increased mucociliary clearance.

Inhaled terbutaline acts within a few minutes and has a duration for up to 6 hours. BRICASMA solution for nebulization is to be used in nebulizers with or without assisted breathing in acute or subacute disorders where conventional inhalers prove unsatisfactory, and in maintenance therapy in severe broncho-obstructive condition.

BRICASMA solution for nebulization is ready for use without dilution. BRICASMA solution for nebulization is isotonic and contains no preservatives.

Pharmacokinetic properties
Terbutaline is metabolized mainly by conjugation with sulphuric acid and excreted as the sulphate conjugate. No active metabolites are formed.

List of excipients
Sodium chloride, disodium edetate, hydrochloric acid, water.

Incompatibilities
BRICASMA solution for nebulization should not be mixed with alkaline solution i.e. solution with a pH higher than 7.0.

Special precautions for storage
Store below 30^{O}C. Do not refrigerate. Protect the ampoules from light.

Shelf-life
Please see outer pack.

Each single dose unit must be used within 24 hours after it is opened. Once the container has been opened, any remaining product cannot be regarded as sterile. This must be considered if the intention is to use the remaining content at a later occasion.

HARUS DENGAN RESEP DOKTER

Pack size
Box of 4 packs of aluminium foil @ 5 respules @ 2 ml (Reg. No.: DKI1151302768A1)

Manufactured by:
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Imported by:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Date of revision text
Approval date:
ANGEL Doc. ID: Doc ID-005037228

Proposed packaging material		
Code	BRICASMA RESPULES 2.5 mg/ml-PIL-01.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: MU-131610-159730	
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Name & Date	FR (24 November 2022)	

Leaflet Informasi untuk Pasien
Bricasma Respules® 2.5 mg/mL
cairan inhalasi oral
terbutalin sulfat
steril

BRICASMA RESPULES adalah sediaan larutan steril yang diubah menjadi uap oleh nebulizer sehingga mudah dihirup ke dalam paru-paru.

BRICASMA RESPULES ditujukan untuk melebarkan saluran nafas pada penyakit paru dimana terjadi penyempitan saluran nafas. Penggunaan sesuai dengan instruksi dokter, hanya digunakan saat diperlukan.

Dosis yang direkomendasikan untuk penggunaan BRICASMA RESPULES adalah 1 respule sebanyak 2 – 4 kali sehari untuk penggunaan pada orang dewasa.

Apabila Anda lupa menggunakan satu dosis penggunaan BRICASMA RESPULES, maka gunakan segera setelah Anda ingat. Namun, jika sudah mendekati jadwal penggunaan dosis berikutnya, maka dosis yang terlupa dapat dilewati. Anda dapat menggunakan dosis berikutnya tepat pada waktunya. Jangan gunakan dosis ganda untuk mengganti dosis yang terlupa.

Beritahu dokter atau apoteker apabila Anda menggunakan BRICASMA RESPULES dengan dosis yang terlalu banyak, tidak sesuai dengan dosis yang dianjurkan.

Jangan gunakan BRICASMA RESPULES apabila Anda memiliki riwayat alergi terhadap terbutaline sulfate dan atau bahan-bahan lain yang terkandung dalam obat ini (natrium klorida, disodium edetate, asam hidroklorat, dan air).

Penggunaan BRICASMA RESPULES harus diperhatikan pada pasien dengan penyakit jantung (termasuk gangguan irama jantung, penyumbatan pada pembuluh darah jantung, gagal jantung, dan penyakit jantung lainnya), pembuluh darah (termasuk darah tinggi), juga penggunaan bersamaan dengan obat-obat yang mempengaruhi kerja jantung. Perlu diperhatikan pula penggunaan pada pasien dengan penyakit kencing manis, riwayat kejang, dan hipertiroid (tingginya kadar hormon kelenjar gondok).

Beri tahu dokter atau apoteker apabila Anda sedang menggunakan, akan menggunakan, atau telah menggunakan obat lain selain BRICASMA RESPULES. Termasuk obat yang dibeli tanpa resep maupun obat herbal. Terutama apabila Anda menggunakan obat steroid (misalnya prednisolone), xantin (misalnya teofilin), diuretik (misalnya furosemide), dan *beta blocker* (misalnya atenolol atau propranolol) termasuk dalam bentuk tetes mata (misalnya timolol).

Bila pada penggunaan terjadi efek samping, seperti nyeri dada, jantung berdebar, sesak napas, sakit kepala, kejang otot, dan gemetar, atau keluhan lain, segera hubungi dokter Anda.

Manfaat dan keamanan BRICASMA RESPULES untuk anak di bawah 12 tahun belum diketahui.

Komunikasikan pada dokter atau apoteker apabila Anda sedang hamil, menyusui, atau berencana untuk hamil selama penggunaan BRICASMA RESPULES.

BRICASMA RESPULES tidak mempengaruhi kemampuan mengendarai kendaraan bermotor maupun menjalankan mesin.

Petunjuk Penggunaan

BRICASMA RESPULES harus digunakan sesuai kebutuhan, bukan untuk penggunaan harian. Jika Anda juga diresepkan obat anti-inflamasi harian untuk asma (seperti kortikosteroid atau antagonis leukotrien inhalasi) Anda harus melanjutkan penggunaannya walaupun Anda sudah tidak membutuhkan penggunaan BRICASMA RESPULES.

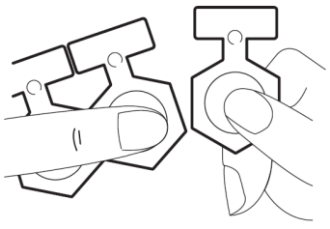
Penggunaan BRICASMA RESPULES saja untuk penanganan asma tanpa terapi tambahan lain (seperti kortikosteroid inhalasi) dapat meningkatkan risiko serangan asma berat.

Segera cari pertolongan medis jika gejala asma Anda (kesulitan bernapas, mengi, atau dada sesak) memburuk atau jika Anda sangat kesulitan bernapas untuk berbicara, makan, ataupun tidur.

Penggunaan harian berlebih BRICASMA RESPULES harus dihindari karena dapat meningkatkan risiko serangan asma yang mungkin mengancam nyawa atau bahkan fatal. Anda mungkin memerlukan obat tambahan untuk mengontrol asthma Anda. Segera hubungi dokter jika anda membutuhkan BRICASMA RESPULES dengan dosis yang lebih tinggi dari biasanya untuk mengatasi gangguan pernapasan Anda.

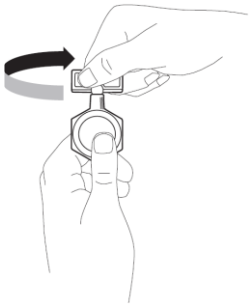
BRICASMA RESPULES hanya digunakan dengan alat nebulizer. Pastikan Anda paham penggunaan alat tersebut sebelum penggunaan BRICASMA RESPULES.

1. BRICASMA RESPULES dikemas dalam kemasan aluminium foil yang berisi 5 respul. Kemasan aluminium foil dibuka saat anda akan menggunakan BRICASMA RESPULES. Untuk setiap penggunaan, ambil 1 respul. (Gambar 1) Kembalikan respul yang belum dibuka pada kemasan aluminium foil sebelum penyimpanan.



Gambar 1

2. Pegang bagian atas respul BRICASMA RESPULES dan putar bagian atas respul untuk membuka seperti ditunjukkan pada Gambar 2.



Gambar 2

3. Tuang seluruh isi respul ke dalam wadah nebulizer seperti ditunjukkan pada Gambar 3. Respul yang telah dibuka masih dapat digunakan dalam waktu 24 jam. Buang respul kosong.

Gambar 3

4. Gunakan nebulizer sesuai petunjuk

Simpan BRICASMA RESPULES pada suhu di bawah 30°C. Jangan disimpan di dalam lemari pendingin. Hindarkan BRICASMA RESPULES dari cahaya.

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
AstraZeneca AB, SE-151 85 Södertälje, Swedia.

Diimpor oleh:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Informasi lebih lanjut dapat menghubungi
PT AstraZeneca Indonesia
Perkantoran Hijau Arkadia Tower F, 3rd Floor
Jl. TB Simatupang Kav. 88 Jakarta 12520 –Indonesia
Telephone: +62 21 2997 9000

Nomor Izin Edar: DKI1151302768A1
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