PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

BUDAIR 0,25 mg/ml (Nebuliser Suspension)

BUDAIR 0,5 mg/ml (Nebuliser Suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BUDAIR 0,25 mg/ml

Each ampoule contains 0,5 mg of budesonide.

Sugar free

BUDAIR 0,5 mg/ml

Each ampoule contains 1,0 mg of budesonide.

Sugar free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Sterile nebuliser suspension. Off white coloured aqueous

suspension, filled in 2 ml unit dose translucent plastic ampoule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

BUDAIR is indicated for management of asthma in patients inadequately controlled by bronchodilators, thus necessitating additional treatment with steroids and who are unable to use a pressurised metered dose inhaler or unable to inhale the medicine in powder form.

BUDAIR is also recommended for use in infants and children with acute laryngotracheobronchitis-croup.

4.2. Posology and method of administration

Instruction for correct use of BUDAIR:

BUDAIR should be administered via a jet nebuliser equipped with a mouthpiece or suitable face mask. The nebuliser should be connected to an air compressor with an adequate air flow (5-8 litres/minute), and the fill volume should be 2-4 ml.

Ultrasonic nebulisers are not suitable for the administration of **BUDAIR** and therefore are not recommended.

For complete instructions for the correct use of BUDAIR please refer to the accompanying patient information leaflet.

The dosage of **BUDAIR** nebulizing suspension is individual, and should be titrated to the lowest effective maintenance dose once the control of asthma is achieved.

Asthma

Adults

Initial Dose:

0,5-1 mg twice daily. In some cases, the dose may be further increased.

Children	***12 months-6 years***	***6 years and older***
Previous therapy	***Recommended starting dose***	
Bronchodilators alone	0,25 mg twice daily	0,25-0,5 mg twice daily
Inhaled corticosteroids	0,25 mg twice daily	0,25-0,5 mg twice daily
Oral corticosteroids	0,5 mg twice daily	0,25-1 mg twice daily
Maintenance dose	0,25-0,5 mg twice daily	

In patients where an increased therapeutic effect is required, an increased dose of **BUDAIR** should be considered.

Maintenance dose:

The maintenance dose is individual. After the desired clinical effect has been obtained, the maintenance dose should be gradually reduced to the smallest amount necessary to control symptoms.

Patients dependent on oral steroids

Initially, **BUDAIR** should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately 1 week the oral dose is gradually reduced to the lowest possible level, e.g. by about 2,5 mg prednisolone every two weeks. A slow rate of withdrawal is strongly recommended.

In a proportion of cases, it is possible to completely substitute the oral glucocorticosteroid with **BUDAIR**.

During withdrawal some patients may experience symptoms of systemic corticosteroid withdrawal, e.g. joint and/or muscle pain, lassitude and depression, despite maintenance or even in improvement in pulmonary function. Such patients should be encouraged to continue with **BUDAIR**

but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should be continued more slowly. During periods of stress or during a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

Acute laryngotracheobronchitis croup

In infants and children with croup, the usual dose is 2 mg of nebulised budesonide. This dose is given as a single administration or as two 1 mg doses separated by 30 minutes.

Dosage table

Dosage in mg	**Volume of BUDAIR**	
	0,25 mg/ml	**0,5 mg/ml**
0,25 mg	1 ml	-
0,5 mg	2 ml	1 ml
0,75 mg	3 ml	-
1 mg	-	2 ml
1,5 mg	-	3 ml
2 mg	-	4 ml

BUDAIR can be mixed with 0,9 % saline and with solutions for nebulisation of terbutaline, salbutamol, fenoterol, acetylcysteine, sodium cromoglycate or ipratropium bromide. The admixture should be used within 30 minutes.

4.3. Contraindications

BUDAIR is contraindicated in:

- Hypersensitivity to budesonide and any of the ingredients of BUDAIR listed in section 6.1.

- Lung tuberculosis, fungal and viral infection in airways

Safety and efficacy for children less than 12 months has not been established.

4.4. Special warnings and precautions for use

Facial skin irritation may occur when a nebuliser with face mask is used. To prevent irritation, the facial skin should be washed with water after use of face mask. To minimize oropharyngeal thrush, the patient should rinse the mouth out with water after each dosing occasion.

BUDAIR is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required.

If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for increased anti-inflammatory therapy, e.g. higher doses of inhaled budesonide or a course of oral glucocorticosteroid.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time. Patients who have required high dose emergency corticosteroid therapy or prolonged treatment at the highest recommended dose of inhaled corticosteroids may also be at risk. These patients may exhibit signs and symptoms of adrenal insufficiency when exposed to severe stress. Additional systemic corticosteroid cover should be

considered during periods of stress or elective surgery.

Systemic effects may occur with any inhaled corticosteroids, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children (see section 4.8). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Some patients feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. A general insufficient glucocorticosteroid effect should be suspected if symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary.
Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by systemic medicine. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Reduced liver function may affect the elimination of corticosteroids. This may be clinically relevant in patients with severely compromised liver function.

The plasma clearance following an intravenous dose of budesonide was reported to be similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of budesonide was reported to increase by compromised liver function due to decreased first pass metabolism. The

clinical relevance of this to treatment with budesonide is unknown as no reported data exist for inhaled budesonide, but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected.

The long- term local and systemic effects of **BUDAIR** in human subjects are not completely known. The dose should be titrated to the lowest effective maintenance dose once control of asthma is achieved. Medical practitioners should closely monitor the growth of children and adolescents taking corticosteroids by any route and weigh the benefit of corticosteroid therapy and asthma control against the possibility of growth suppression.

Special consideration may be needed in patients with active or quiescent pulmonary tuberculosis (see **section 4.3**)

Non steroid-dependent patients: A therapeutic effect is usually reached within 10 days. In patients with excessive mucus secretion in the bronchi, a short (about 2 weeks) additional oral corticosteroid regimen can be given initially. After the course of the oral medicine, **BUDAIR** alone should be sufficient therapy.

Steroid-dependent patients: When transfer from oral corticosteroid to treatment with **BUDAIR** is initiated, the patient should be in a relatively stable phase. **BUDAIR** is then given, in combination with the previously used oral steroid dose, for about 10 days.

After that, the oral steroid dose should be gradually reduced (by, for example, 2,5 mg prednisolone or the equivalent each month), to the lowest possible level. In many cases, it is possible to completely substitute **BUDAIR** for the oral corticosteroid.

On prolonged administration signs or symptoms of systemic glucocorticosteroid effect, including hypofunction of adrenal gland and reduction of growth velocity, may occur with inhaled glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.

Paradoxical bronchospasm may occur. (see **section 4.8**).

Co-treatment with CYP3A inhibitors, e.g. itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products is expected to increase the risk of systemic corticosteroid side effects. Therefore, the combination should be avoided unless the benefit outweighs this increased risk, in which case patients should be monitored for systemic corticosteroid side effects. This is of limited clinical importance for short-term (1-2 weeks) treatment with itraconazole or ketoconazole or other potent CYP3A inhibitors, but should be taken into consideration during long-term treatment. A reduction in the dose of budesonide should also be considered (see **section 4.5**).

The nebuliser chamber should be cleaned after every administration. Wash the nebuliser chamber and mouthpiece or face-mask in hot water using a mild detergent. Rinse well and dry, by connecting the nebuliser chamber to the compressor or air inlet.

Oral candidiasis may occur during the therapy with inhaled corticosteroids. This infection may require treatment with appropriate antifungal therapy and in some patients discontinuation of treatment may be necessary.

Pneumonia in patients with chronic obstructive pulmonary disorder (COPD)

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been reported in patients with COPD receiving inhaled corticosteroids. There is some reported evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive reported clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid medicines.
Medical practitioners should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.
Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids (see section 4.8).

Paediatric population

Influence on growth

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid, if possible, to the lowest dose at which effective

control of asthma is maintained. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition, consideration should be given to referring the patient to a paediatric respiratory specialist.

4.5. Interaction with other medicines and other forms of interaction

Budesonide has not been reported to interact with any medicine used for the treatment of asthma.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibitors of this enzyme, e.g. ketoconazole, itraconazole, HIV protease inhibitors and cobicistat-containing medicines therefore increase systemic exposure to budesonide and are expected to increase the risk of systemic side effects (see section 4.4. and 5.2).

The combination of **BUDAIR** with potent CYP3A inhibitors should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. If **BUDAIR** is co-administered with anti-fungals (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the **BUDAIR** dose could be considered.

Limited reported data about this interaction for high-dose inhaled budesonide indicate that marked increases in plasma levels (on average four--fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).

Raised plasma concentrations of and enhanced effects of corticosteroids have been reported in women also treated with oestrogens and contraceptive steroids, but no effect has been reported with budesonide and concomitant intake of low dose combination oral contraceptives.

Because adrenal function may be suppressed, an (Adrenocorticotropic hormone) (ACTH) stimulation test for diagnosing pituitary insufficiency might show false results (low values).

At recommended doses, cimetidine has slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Paediatric population

Interaction studies have only been reported in adults.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been reported.

It is important for both foetus and mother to maintain an adequate asthma treatment during pregnancy.

Inhaled glucocorticosteroids should be considered in preference to oral glucocorticosteroids because of the lower systemic effects at the doses required to achieve similar pulmonary responses.

Breastfeeding

Safety in lactation has not been reported.

Budesonide is excreted in breast milk. However, at maternal therapeutic doses of **BUDAIR**, the

budesonide plasma level in infants are at or below minimal measurable concentrations.

Fertility

There are no fertility data reported for budesonide.

4.7. Effects on ability to drive and use machines

BUDAIR has no effect on ability to drive and use machines.

However blurred vision may occur, and patient should be advised not to drive or operate machines until they know how **BUDAIR** affects them.

4.8. Undesirable effects

The following adverse events have been reported from clinical studies and post-marketing experience by system organ class and frequency.

Table: Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

SOC	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	Frequent	Oropharyngeal candidiasis Pneumonia (in COPD patients)
Immune system disorders	Less frequent	Immediate and delayed hypersensitivity reactions* including rash, bronchospasm, contact dermatitis, urticaria, angioedema and anaphylactic reaction
Endocrine disorders	Less frequent	Signs and symptoms of systemic corticosteroid effects, including adrenal suppression and growth retardation**
Psychiatric disorders	Less frequent	Anxiety, depression, psychomotor hyperactivity, sleep disorders, aggression, behavioural changes

		(predominantly in children)
	Frequency not known	Nervousness, restlessness
Nervous system disorders	Less frequent	Tremor***
Eye disorders	Less frequent	Cataract, blurred vision (see also **section 4.4**)
	Frequency not known	Glaucoma
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing
		Hoarseness
		Throat irritation
	Less frequent	Bronchospasm, Dysphonia, hoarseness****
Skin and subcutaneous tissue disorders	Less frequent	Bruising
Musculoskeletal and connective tissue disorders	Less frequent	Muscle spasm

* refer to Description of selected adverse reactions; facial skin irritation, below

** refer to Paediatric population, below

*** based on the frequency reported in clinical trials

**** rare in children

Occasionally, signs or symptoms of systemic glucocorticosteroid-side effects may occur with inhaled

glucocorticosteroids, probably depending on dose, exposure time, concomitant and previous corticosteroid exposure, and individual sensitivity (see **section 4.4**).

Description of selected adverse reactions

The candida infection in the oropharynx is due to the medicine deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk.

Paradoxical bronchospasm may occur. (see **section 4.4**).

Facial skin irritation, as an example of a hypersensitivity reaction, has been reported in some cases when a nebuliser with a face mask has been used (see section 4.4). To prevent irritation, the facial skin should be washed with water after use of the face mask.

Paediatric population

Due to the risk of growth retardation in the paediatric population, growth should be monitored as described in **section 4.4**.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reaction Reporting form'**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8.

4.9. Overdose

Acute overdosage with **BUDAIR**, even in excessive doses, is not expected to be a clinical problem. Treatment should be discontinued and appropriate measures taken to protect the patient against stress situations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.5.1 Corticosteroids and analogues

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, glucocorticoids.

ATC Code: RO3B A02

Pharmacodynamic properties

Budesonide is a glucocorticosteroid with local anti-inflammatory effect.

The exact mechanism of action of glucocorticosteroids in the treatment of asthma is not fully understood. Anti-inflammatory actions involving T-cells, eosinophils and mast cells, such as inhibition of inflammatory mediator release and inhibition of cytokine-mediated immune response are probably important.

The therapeutic effect of conventional doses of inhaled budesonide may be largely explained by its direct action on the respiratory tract.

Budesonide has been reported to decrease airway reactivity to histamine and methacholine in hyper-reactive patients.

5.2. Pharmacokinetic properties

Absorption

In adults the systemic availability of budesonide following administration of budesonide via a jet nebuliser is reported to be approximately 15 % of the nominal dose and 40-70 % of the dose delivered to the patients. A minor fraction of the systemically available medication comes from swallowed budesonide. The maximal plasma concentration, occurring about 10-30 minutes after start of nebulisation is approximately 4 nmol/litre after a single dose of 2 mg.

Distribution

Budesonide has a volume of distribution of approximately 3 litres/kg. Plasma protein binding averages 85-90 %.

Biotransformation

Budesonide undergoes an extensive degree (≈ 90 %) of
biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxybudesonide and 16-alpha-hydroxyprednisolone, is less than 1 % of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Elimination

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1,2 litres/min) in healthy adults and the terminal half-life of budesonide after i.v. dosing averages 2-3 hours.

Linearity

The kinetics of budesonide are dose-proportional at clinically relevant doses.

Children:

In 4-6 years old asthmatic children, the systemic availability of budesonide following administration of **BUDAIR** via a jet nebuliser is reported to be approximately 6 % of the nominal dose and 26 % of the dose delivered to the patients. The systemic availability in children is about half that in healthy adults. The maximal plasma concentration, occurring approximately 20 minutes after start of nebulisation is approximately 2,4 nmol/litre in 4-6 years old asthmatic children after a 1 mg dose.

Budesonide has a systemic clearance of approximately 0,5 litres/min in 4-6 years old asthmatic children. Per kilogram body weight children have a clearance which is approximately 50 % greater than in adults. The terminal half-life of budesonide after inhalation is approximately 2,3 hours in asthmatic children. This is about the same as in healthy adults.

The exposure (C_{max} and AUC) of budesonide following administration of a single 1 mg dose by nebulisation to 4-6 year old children is reported to be comparable to that in healthy adults given the same delivered dose by the same nebulising system.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Edetate Sodium

Polysorbate 80

Sodium chloride

Sodium citrate

Nitrogen

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 30 °C. Always store unopened ampoules in the aluminium pouch in order to protect from light. Ampoules in an open pouch should be used within 3 months.

If you do not use a full ampoule for each dose, store the opened ampoule upright and protected from light. The remaining suspension in an opened ampoule should be used within 12 hours.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Each plastic ampoule contains 2 ml off white coloured aqueous suspension. Strips of 5 ampoules are packed in a sealed printed aluminium pouch. Four aluminium pouches are packed in a printed unit carton of 20 ampoules.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

BUDAIR 0,25 mg/ml: 53/21.5.1/0237

BUDAIR 0,5 mg/ml: 53/21.5.1/0238

9 DATE OF FIRST AUTHORISATION

6 September 2022

10 DATE OF REVISION OF THE TEXT

6 September 2022