PROFESSIONAL INFORMATION FOR

BUDESONIDE RESPULES CIPLA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BUDESONIDE 0,125 mg / mL RESPULES CIPLA

BUDESONIDE 0,25 mg / mL RESPULES CIPLA

BUDESONIDE 0,5 mg / mL RESPULES CIPLA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BUDEFLAM 0,125 mg / mL RESPULES. Each 2 mL ampoule contains 0,25 mg of budesonide.

BUDESONIDE 0,25 mg / mL RESPULES CIPLA. Each 2 mL ampoule contains 0,5 mg of budesonide.

BUDESONIDE 0,5 mg / mL RESPULES CIPLA. Each 2 mL ampoule contains 1 mg of budesonide.

Sugar free.

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

3. PHARMACEUTICAL FORM

Sterile nebuliser suspension.

White to off-white, homogenous redispersible suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BUDESONIDE RESPULES CIPLA 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.

BUDESONIDE RESPULES CIPLA Nebuliser Suspension is also recommended for use in infants and children with acute laryngotracheobronchitis-croup.

4.2 Posology and method of administration

Asthma

Adults:

Initial Dose:

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

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

In patients where an increased therapeutic effect is required, an increased dose of BUDESONIDE RESPULES CIPLA 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, BUDESONIDE RESPULES CIPLA 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 2 weeks. A slow rate of withdrawal is strongly recommended.

In a proportion of cases, it is possible to completely substitute the oral glucocorticosteroid with BUDESONIDE RESPULES CIPLA.

During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with BUDESONIDE RESPULES CIPLA 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 BUDESONIDE RESPULES CIPLA**				
	0,125 mg / mL (1 ampoule = 0,25 mg / 2mL)		**0.25 mg/mL (1 ampoule = 0,5 mg / 2mL)**		**0.5 mg / mL (1 ampoule = 1mg / 2mL)**
0.25 mg	2 mL (1 ampoule)				
0.5 mg*	4 mL (2 ampoules)	or	2 mL (1 ampoule)		
0.75 mg**	2 mL (1 ampoule)	plus	2 mL (1 ampoule)		
1 mg***			4 mL (2 ampoules)	or	2 mL (1 ampoule)
1.5 mg****			2 mL (1 ampoule)	plus	2 mL (1 ampoule)
2 mg					4 mL (2 ampoules)

* **Eithe**r Two ampoules of BUDESONIDE 0.25 mg / 2 mL RESPULES CIPLA **or** one ampoule of BUDESONIDE 0.5 mg / 2 mL RESPULES CIPLA

** One ampoule of BUDESONIDE 0.25 mg / 2 mL RESPULES CIPLA **plus** one ampoule of BUDESONIDE.0,5 mg / 2 mL RESPULES CIPLA

*** **Either** two ampoules of BUDESONIDE 0.5 mg / 2 mL RESPULES CIPLA **or** one ampoule of BUDESONIDE 1 mg / 2 mL RESPULES CIPLA

**** One ampoule of BUDESONIDE 0.5 mg / 2 mL RESPULES CIPLA **plus** one ampoule of BUDESONIDE 1 mg / 2 mL RESPULES CIPLA

BUDESONIDE RESPULES CIPLA 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.

Method of administration:

Instruction for correct use of BUDESONIDE RESPULES CIPLA:

BUDESONIDE RESPULES CIPLA 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 to 8 litres/minute), and the fill volume should be 2 to 4 mL

Ultrasonic nebulisers are not suitable for the administration of BUDESONIDE RESPULES CIPLA and therefore are not recommended.

The dosage of BUDESONIDE RESPULES CIPLA is individual and should be titrated to the lowest effective maintenance dose once control of asthma is achieved.

4.3 Contraindications

BUDESONIDE RESPULES CIPLA is contraindicated in:

- Patients with known hypersensitivity to budesonide or to any of the excipients in BUDESONIDE RESPULES CIPLA (see **section 6.1**).
- Patients with lung tuberculosis, fungal and viral infections in the airways.
- Safety and efficacy for children less than 12 months have not been established.
- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

4.4 Special warnings and precautions for use

Special consideration may be needed in patients with active or quiescent pulmonary tuberculosis and in patients with fungal or viral infections in the airways.

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, BUDESONIDE RESPULES CIPLA alone should be sufficient therapy.

Steroid-dependent patients

When transfer from oral corticosteroid to treatment with BUDESONIDE RESPULES CIPLA is initiated, the patient should be in a relatively stable phase. BUDESONIDE RESPULES CIPLA 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 BUDESONIDE RESPULES CIPLA for the oral corticosteroid.

Replacement of systemic steroid treatment with inhaled therapy sometimes unmasks allergies, e.g., rhinitis and eczema, which were previously controlled by the systemic medicine. These allergies should be symptomatically controlled with an antihistamine and/or topical preparations.

Particular care is needed in patients transferring from oral steroids, since they may remain at risk of impaired adrenal function for a considerable time.

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.

Paradoxical bronchospasm may occur, manifested by an immediate increase in wheezing after dosing. If this occurs, treatment with inhaled budesonide should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.

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 corticosteroid, 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 less frequently, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

BUDESONIDE RESPULES CIPLA 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.

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 however can be similar in cirrhotic patients and in healthy subjects. After oral ingestion systemic availability of budesonide can be increased by compromised liver function due to decreased first pass metabolism. The relevance of this to treatment with BUDESONIDE RESPULES CIPLA is unknown as no data exist for inhaled budesonide but increases in plasma levels and hence an increased risk of systemic adverse effects could be expected.

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 to 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 facemask 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 patient's discontinuation of treatment may be necessary (see also **section 4.2**).

To minimise oral candidiasis, the patient should rinse the mouth out with water after each occasion.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, can be observed in patients with COPD receiving inhaled corticosteroids. Increased risk of pneumonia with increasing steroid dose can be observed in some patients with COPD. There is no conclusive evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Medical practitioners should remain vigilant for the possible development of pneumonia in patients with COPD as the 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 serious chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Facial skin irritation:

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 the face mask. To minimise oropharyngeal thrush, the patient should rinse the mouth out with water after each dosing occasion.

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.

The long-term local and systemic effects of BUDESONIDE RESPULES CIPLA 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.

4.5 Interaction with other medicines and other forms of interaction

Budesonide has not been observed 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 and itraconazole, therefore increase systemic exposure to budesonide.

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

The combination of BUDESONIDE RESPULES CIPLA 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 BUDESONIDE RESPULES CIPLA is co-administered with anti-fungal (such as itraconazole and ketoconazole), the period between treatments should be as long as possible. A reduction of the budesonide dose could be considered.

Few Incidents 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 can be observed in women also treated with oestrogens and contraceptive steroids, but no effect has been observed with budesonide and concomitant intake of low dose combination oral contraceptives.

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

Paediatric population

The interaction of BUDESONIDE RESPULES CIPLA with other medicines and other forms of interaction in the paediatric population has not been established.

4.6 Fertility, pregnancy, and lactation

Pregnancy:

Safety in pregnancy has not been established.

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 breastfeeding has not been established. Budesonide is excreted in breast milk. However, at maternal therapeutic doses of BUDESONIDE RESPULES CIPLA, the budesonide plasma levels in infants are at or below minimal measurable concentrations.

4.7 Effects on ability to drive and use machines

BUDESONIDE RESPULES CIPLA has no effect on the ability to drive and use machines.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

Table 1: Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

MedDRA system organ class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Oropharyngeal candidiasis Pneumonia (in COPD patients)

MedDRA system organ class	Frequency	Side effects
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 unknown	Nervousness, restlessness
Nervous system disorders	Less frequent	Tremor ***
Eye Disorders	Less frequent	Cataract, Vision, blurred (see also **section 4.4**)
	Frequency unknown	Glaucoma
Respiratory, thoracic and mediastinal disorders	Frequent	Hoarseness, cough, throat irritation
	Less frequent	Dysphonia, hoarseness****
Skin and subcutaneous tissue disorders	Less frequent	Bruising
Musculoskeletal and connective tissue disorders	Less frequent	Muscle Spasms

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

** refer to Paediatric population, below

*** based on the frequency reported in clinical trials

**** less frequent 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 medicine deposition. Advising the patient to rinse the mouth out with water after each dosing will minimise the risk.

Paradoxical bronchospasm may occur in less frequent cases (see **section 4.4**).

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 the face mask. To minimise oropharyngeal thrush, the patient should rinse the mouth out with water after each dosing occasion.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA

website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

Acute overdose with BUDESONIDE RESPULES CIPLA, even in excessive doses, is not expected to constitute a medical problem.

Treatment should be discontinued, and appropriate measures should be taken to protect the patient against stress situations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.5.1 Corticosteroids and analogues

ATC code: R03 BA02:

Pharmacotherapeutic group: Other medicines for obstructive airways diseases, inhalant, Glucocorticoids.

Mechanism of action

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 shown 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 nebulizer is approximately 15 % of the nominal dose and 40 % to 70 % of the dose delivered to the patients. A minor fraction of the systemically available medicine comes from swallowed medicine The maximal plasma concentration, occurring about 10 to 30 minutes after start of nebulisation is approximately 4 nmol/L after a single dose of 2 mg.

Distribution

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85 to 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-betahydroxybudesonide 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 high

systemic clearance (approximately 1,2 L/min) in healthy adults and the terminal half-life of budesonide after IV dosing averages 2 to3 hours.

Linearity/non-linearity

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

When 100 mg ketoconazole is taken twice daily, increased plasma levels of concomitantly administered oral budesonide (single dose of 10 mg) on average, by 7,8-fold. Information about this interaction is lacking for inhaled budesonide but marked increases in plasma levels could be expected.

Paediatric population

In 4 to 6 years old asthmatic children, the systemic availability of budesonide following administration of budesonide via a jet nebuliser is 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/L in 4 to 6 years old asthmatic children after a 1 mg dose.

Budesonide has a systemic clearance of approximately 0,5 L / min in 4 to 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 to 6 year-old children is 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 (E330)

Edetate Disodium

Polysorbate 80 (E433)

Sodium Chloride

Sodium citrate (Dihydrate) (E331)

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 keep unopened single dose units in the foil envelope so they are well protected from light. Single units in an open foil envelope should be used within 3 months. If you do not use a full unit for each dose, store the opened container protected from light. The contents of an opened container should be used within 12 hours. Keep out of reach of children.

6.5 Nature and contents of container

BUDESONIDE RESPULES CIPLA is packed in Form Fill Seal (FFS) ampoules (vials) made up of low-density polyethylene granules containing 2 mL of inhalation suspension. Sheets of 5 ampoules are packed in triple laminated film/foil envelope (protective packaging). 4 such envelopes are packed per unit carton.

1's pack: Carton containing Triple laminated pouch having 1 respule of 2 ml.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Belville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER

BUDEFLAM 0,125 mg / mL RESPULES: 57/21.5.1/0004.001

BUDESONIDE 0,25 mg / mL RESPULES CIPLA: 57/21.5.1/0005.002

BUDESONIDE 0,5 mg / mL RESPULES CIPLA: 57/21.5.1/0006.003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 18 March 2025

Latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable