PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

BUDONEB 0,25 mg/ml (nebuliser suspension)

BUDONEB 0,5 mg/ml (nebuliser suspension)

COMPOSITION:

BUDONEB is an aqueous suspension of budesonide buffered to pH 4,5.

BUDONEB 0,25 mg/ml (2 ml/ampoule): Each ml contains 0,25 mg of budesonide.

BUDONEB 0,5 mg/ml (2 ml/ampoule): Each ml contains 0,5 mg of budesonide.

The other ingredients are:

Citric acid, anhydrous, disodium edetate, polysorbate 80, sodium chloride, sodium citrate, water for injection.

BUDONEB is sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A.21.5.1 Corticosteroids and analogues

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Budesonide is a glucocorticosteroid with local anti-inflammatory effects. 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. Budesonide has been shown to decrease airway reactivity to histamine and methacholine in hyperactive patients.

Pharmacokinetic properties:

Absorption

In adults the systemic availability of budesonide following administration of budesonide suspension via a jet nebuliser is approximately 15 % of the nominal dose and 40 - 70 % of the dose delivered to the patients. A minor fraction of the systematically available budesonide comes from the swallowed BUDONEB. The maximal plasma concentration, occurring about 10 – 30 minutes after the 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 – 90 %.

Metabolism

Budesonide undergoes an extensive degree (= 90 %) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of 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 CYP3A4, 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 l/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 budesonide suspension via a jet nebuli is approximately 6 % of the nominal dose and 26 % of the dose delivered to patients. The systemic availability in children is about half of that in healthy adults. The maximal plasma concentration, occurring approximately 20 minutes after the start of nebulisation, is approximately 2,4 nmol/l in 4 – 6 year old asthmatic children after a 1 mg dose.

Budesonide has a systemic clearance of approximately 0,5 l/min in 4 – 6 year old asthmatic children. Per kg 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 years old children is comparable to that in healthy adults given the same nebulising system.

INDICATIONS:

BUDONEB is indicated for:

- Management of asthma in patients inadequately controlled by bronchodilators, thus necessitating treatment with steroids and who are unable to use a pressurised metered dose inhaler or unable to inhale the medicine in powder form.
- BUDONEB is also recommended in infants and children with acute laryngotracheobronchitis (croup).

CONTRAINDICATIONS:

- Hypersensitivity to budesonide or any of the ingredients of BUDONEB.
- Lung tuberculosis, fungal and viral infections in the airways.
- Safety and efficacy for children less than 12 months have not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

BUDONEB 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 glucocorticosteroids.

The long-term local and systemic effects of BUDONEB 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.

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

Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

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 renal 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.
Less frequently, through unknown mechanisms, medicines for inhalation may cause bronchospasm.

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

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

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.

Long-term treatment may induce cataract formation. Referral to a doctor is recommended if a patient presents with symptoms such as blurred vision or other visual disturbances for evaluation of possible causes which may include cataract, glaucoma or diseases such as central serous chorioretinapathy (CSCR).

Effects on ability to drive and use machines

BUDONEB has no effect on the ability to drive and use machines.

Long term use may affect vision.

INTERACTIONS:

BUDONEB has not been observed to interact with any medicine used for the treatment of asthma.

The metabolism of BUDONEB is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibitors of this enzyme, e.g. ketoconazole, itraconazole and cobicistat-containing medicine, therefore increase systemic exposure to BUDONEB. The combination of BUDONEB and cobicistat-containing medicine should be avoided.

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

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Instructions for correct use of BUDONEB:

For use only in a nebuliser. Not to be used for injection.

The ampoule must be swirled before use.

Shake the contents gently using a swirling motion.

Hold the single dose unit upright and open by twisting off the wing.

Place the open end of the unit well into the reservoir of the nebuliser and squeeze slowly.

Single dose units (2 ml/ampoule) remaining in an opened pouch should be used within 3 months.

After use:

Rinse the mouth out with water after inhaling the prescribed dose to minimize the risk of oropharyngeal thrush.

Wash the facial skin with water after using the face mask to prevent irritation.

Cleaning instructions:

Adequately clean and maintain the nebuliser according to the manufacturer's instructions.

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

Asthma:

Adults:

Initial dose:

0,5 to 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**	**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	0,25 – 0,5 mg twice daily

In patients where an increased therapeutic effect is required, an increased dose of BUDONEB 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, BUDONEB should be used concurrently with the patient's usual maintenance dose of oral glucocorticosteroid. After approximately one 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 BUDONEB.

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 BUDONEB 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 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 in mg	**Volume of BUDONEB**	**Volume of BUDONEB**
	0,25 mg/ml **(2 ml/ampoule)**	**0,5 mg/ml** **(2 ml/ampoule)**
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

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

SIDE EFFECTS:

Clinical trials, literature reports and post-marketing experience suggest that the following adverse reactions may occur.

Infections and infestations:

Frequent: Candida infection in the oropharynx.

Immune system disorders:

Less Frequent: Immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm.

Psychiatric disorders:

Less frequent: Nervousness, restlessness, depression, behavioural disturbances.

Respiratory, thoracic and mediastinal disorders:

Frequent: Mild irritation in the throat, hoarseness, coughing.

Skin and subcutaneous tissue disorders:

Less frequent: skin bruising.

Eye disorders

Less frequent: Cataract, vision blurred (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Frequency unknown: Glaucoma.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage with BUDONEB 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.

Treatment is supportive and symptomatic.

IDENTIFICATION:

White to off-white suspension in single-dose plastic ampoule unit with a twist off top, for use in a nebuliser.

PRESENTATION:

3 ml single-dose low density polyethylene polymer, Purell PE 3020 D unit dose ampoules in strips of 5 ampoules per strip, overwrapped in a tri-laminate foil pouch (consists of an outer layer-polyester film, middle layer-aluminium foil and inner layer- polyethylene. One strip is packed per foil pouch. Four foil pouches are packed into an outer carton.

Each carton contains 20 clear, translucent LDPE resin ampoules of 2 ml nebuliser suspension.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep unused ampoules in the pouch. Once the pouch is opened, the unused ampoules must be protected from light by keeping the pouch closed.

The ampoules in the opened pouches should be used within three months from date of first opening the pouch.

The ampoule must be swirled before use.

The ampoule once opened will not be re-used again. Any suspension not used immediately should be discarded.

Keep out of reach of children.

REGISTRATION NUMBER:

BUDONEB 0,25 mg/ml: 42/21.5.1/0953

BUDONEB 0,5 mg/ml: 42/21.5.1/0954

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

DATE OF PUBLICATION OF PROFESSIONAL INFORMATION:

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