PROFESSIONAL INFORMATION FOR

BUDENOFALK 3 mg (CAPSULES)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BUDENOFALK 3 mg CAPSULES.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 3 mg budesonide as the active ingredient

The product contains sugar

Lactose monohydrate: 12 mg/capsule

Sucrose: 276 mg/capsule

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Pink capsules (size 1) containing white round pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Crohn’s disease

Induction of remission in patients with mild to moderate active Crohn’s disease affecting the ileum and/or the ascending colon.

For the induction and maintenance of remission in patients with:

- Microscopic colitis
- Autoimmune hepatitis

4.2 Posology and method of administration

Posology

Crohn's disease

Induction of remission

The recommended daily dose is three capsules once daily in the morning or one capsule (containing 3 mg budesonide) three times daily (morning, midday and evening; corresponding to a total daily dose of 9 mg budesonide) if this is more convenient to the patient about ½ hour before meals.

Duration of treatment

The duration of treatment in active Crohn's Disease should be limited to 8 weeks.

Microscopic colitis

Induction of remission

The recommended dose is three capsules once daily in the morning (corresponding to a daily dose of 9 mg budesonide).

Maintenance of remission

Maintenance therapy should only be initiated in patients with frequently recurring symptoms of microscopic colitis after successful induction treatment. A dosage regimen of two capsules once daily in the morning (6 mg budesonide) or of two capsules once daily in the morning alternating with one capsule daily in the morning (corresponding to an average

daily dose of 4.5 mg budesonide) can be applied, according to the individual requirements of the patient. The lowest effective dose should be used.

Duration of treatment

The duration of treatment in active microscopic colitis should be limited to 8 weeks.
In maintenance therapy, the treatment effect should be evaluated regularly to assess if continued treatment is necessary, not later than 12 months after the initiation of maintenance treatment. Maintenance treatment should only be extended beyond a duration of 12 months if the benefits for the individual patient are considered to outweigh the risks.

Autoimmune hepatitis

Induction of remission

For the induction of remission (i.e. normalisation of elevated laboratory parameters) the recommended daily dose is one capsule (containing 3 mg budesonide) three times daily (morning, midday and evening; corresponding to a total daily dose of 9 mg budesonide).

Maintenance of remission

After achievement of remission the recommended daily dose is one capsule (containing 3 mg budesonide) twice daily (one capsule in the morning and one capsule in the evening; corresponding to a total daily dose of 6 mg budesonide).
If the transaminases ALAT and/or ASAT increase during maintenance treatment, the dose should be increased to 3 capsules per day (corresponding to a total daily dose of 9 mg budesonide) as described for induction of remission.
In patients tolerant to azathioprine, treatment for induction and maintenance of remission with budesonide should be combined with azathioprine.

Duration of treatment

For the induction of remission a total daily dose of 9 mg should be given until remission is achieved. Thereafter, for maintenance of remission a total daily dose of 6 mg budesonide should be given. Treatment for maintenance of remission in autoimmune hepatitis should be continued at least for 24 months. It might be terminated only if biochemical remission is constantly maintained and if no signs of inflammation are present in a liver biopsy.

Termination of treatment

The treatment with BUDENOFALK 3mg CAPSULES should not be stopped abruptly, but withdrawn gradually (tapering doses). Gradual dose reduction over 2 weeks is recommended.

Paediatric population

Children under the age of 12

BUDENOFALK 3 mg CAPSULES should not be taken by children younger than 12 years due to insufficient experience and possibly increased risk of adrenal suppression in this age group.

Adolescent patients aged 12 to 18 years

The safety and efficacy of BUDENOFALK 3 mg CAPSULES in children aged 12 to 18 years have not yet been established. Currently available data in adolescent patients (12 to 18 years) with Crohn's disease or autoimmune hepatitis are described in **sections 4.8 and 5.1** but no recommendation on a posology can be made.

Patients with renal impairment

There are no specific dosage recommendations for patients with renal insufficiency.

Patients with hepatic impairment

Since the information is limited in this patient-population a specific dose recommendation cannot be made.

Method of administration

The capsules should be taken about half an hour before meals, swallowed whole with plenty of fluid (e.g. a glass of water).

4.3 Contraindications

BUDENOFALK 3 mg CAPSULES must not be used in patients with:

- hypersensitivity to budesonide or any of the ingredients listed in section 6.1
- hepatic cirrhosis.

4.4 Special warnings and precautions for use

Treatment with BUDENOFALK 3 mg CAPSULES results in lower systemic steroid levels than conventional oral steroid therapy. Transfer from other steroid therapy may result in symptoms relating to the change in systemic steroid levels. When patients are switched from systemically acting steroids to locally acting budesonide it should be considered that BUDENOFALK 3 mg CAPSULES is not indicated for the treatment of esophageal Crohn´s disease. Caution is required in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, family history of diabetes, family history of glaucoma, or any other condition in which glucocorticoids may have undesirable effects.

Systemic effects of corticosteroids may occur, particularly when prescribed at high doses and for prolonged periods. Such effects may include Cushing’s syndrome, adrenal

suppression, growth retardation, decreased bone mineral density, cataract, glaucoma and very rarely a wide range of psychiatric/behavioural effects **(see section 4.8).**

Live vaccines

Live vaccines should not be given to individuals with chronic corticosteroid use. The antibody response to other vaccines may be diminished.

Infection

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The risk of deterioration of bacterial, fungal, amoebic and viral infections during glucocorticoid treatment should be carefully considered. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked, and therefore may reach an advanced stage before being recognised.

Chickenpox

Chickenpox is of concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. If the patient is a child, parents must be given the above advice. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped, and the dose may need to be increased.

Measles

Patients with compromised immunity who have come into contact with measles should, wherever possible, receive normal immunoglobulin as soon as possible after exposure.

Patients with liver function disorders

Based on the experience with patients suffering from late stage primary biliary cirrhosis (PBC) with hepatic cirrhosis an increased systemic availability of budesonide in all patients with severely impaired hepatic function is to be expected.

However, in patients with liver disease without hepatic cirrhosis budesonide in daily doses of 9 mg was safe and well tolerated. There is no evidence that a specific dose recommendation for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary.

Others

Corticosteroids may cause suppression of the hypothalamus-pituitary-adrenal (HPA) axis and reduce the stress response. When patients are subject to surgery or other stresses, supplementary systemic glucocorticoid treatment is recommended.

Concomitant treatment with ketoconazole or other CYP3A inhibitors should be avoided (see **section 4.5**).

BUDENOFALK 3 mg CAPSULES contain lactose and sucrose. Patients with rare hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, the Lapp lactase deficiency or the congenital lactase deficiency should not take this medicine.

In patients with autoimmune hepatitis, serum transaminase levels (ALT, AST) should be regularly monitored (every 2 weeks for the first month of treatment and at least every 3 months thereafter), in order to facilitate dose adjustments of budesonide.

Administration of the BUDENOFALK 3 mg CAPSULES can lead to positive results in doping tests.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

- *Cardiac glycosides:* The action of the glycoside can be potentiated by potassium deficiency.
- *Saluretics:* Potassium excretion can be enhanced.

Pharmacokinetic interactions:

Cytochrome P450

- *CYP3A4 inhibitors:*
- Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination 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.

  Ketoconazole 200 mg once daily orally increased the plasma concentrations of budesonide (3 mg single dose) approximately 6-fold during concomitant administration. When ketoconazole was administered 12 hours after budesonide, the concentrations increased approximately 3-fold. As there are not enough data to give dose recommendations, the combination should be avoided.
  Other potent inhibitors of CYP3A4 such as ritonavir, itraconazole, clarithromycin, and

grapefruit juice are also likely to cause a marked increase of the plasma concentrations of budesonide. Therefore, concomitant intake of budesonide should be avoided.

- *CYP3A4 inducers:*

  Compounds or agents such as carbamazepine and rifampicin, which induce CYP3A4, may reduce the systemic but also the local exposure of budesonide at the gut mucosa. An adjustment of the budesonide dose may be necessary.

- *CYP3A4 substrates:*

  Compounds or agents which are metabolized by CYP3A4 may be in competition with budesonide. This may lead to an increased budesonide plasma concentration if the competing substance has a stronger affinity to CYP3A4, or – if budesonide binds stronger to CYP3A4 – the competing substance might be increased in plasma and a dose-adaption/reduction of this medicine might be required.

Elevated plasma concentrations and enhanced effects of corticosteroids have been reported in women also receiving oestrogens or oral contraceptives, but this has not been observed with oral low dose combination contraceptives.

Cimetidine at recommended doses in combination with budesonide has a small but insignificant effect on pharmacokinetics of budesonide. Omeprazole has no effect on the pharmacokinetics of budesonide.

Steroid-binding compounds:

In theory, potential interactions with steroid-binding synthetic resins such as cholestyramine, and with antacids cannot be ruled out. If given at the same time as BUDENOFALK 3 mg

CAPSULES, such interactions could result in a reduction in the effect of budesonide. Therefore, these preparations should not be taken simultaneously, but at least two hours apart.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established.

Breast-feeding:

Budesonide is excreted in human milk (data on excretion after inhalative use is available). However, only minor effects on the breast-fed child are anticipated after intake of BUDENOFALK 3 mg CAPSULES within the therapeutic range. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from budesonide therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility:

There are no data on the effect of budesonide on human fertility. Fertility was unaffected following budesonide treatment in animal studies **(**see **section 5.3).**

4.7 Effects on ability to drive and use machines

The effect of BUDENOFALK 3 mg CAPSULES on the ability to drive and use machines is unknown.

4.8 Undesirable effects

Metabolism and nutrition disorders

Frequent: Cushing's syndrome: e.g. with moon face, truncal obesity, reduced glucose tolerance, diabetes mellitus, hypertension, sodium retention with oedema, increased potassium excretion,

inactivity or atrophy of the adrenal cortex, red striae, steroid acne, disturbance of sex hormone secretion (e.g. amenorrhea, hirsutism, impotence)

Less frequent: Growth impairment in children

Eye disorders

Less frequent: Glaucoma, cataract, blurred vision

Gastrointestinal disorders

Less frequent: Gastric complaints, gastroduodenal ulcer, pancreatitis, constipation

Immune system disorders

Frequent: Increased risk of infection

Musculoskeletal and connective tissue disorders

Frequent: Muscle and joint pain, muscle weakness and twitching, osteoporosis

Less frequent: Aseptic necrosis of bone (femur and head of the humerus)

Nervous system disorders

Frequent: Headache

Less frequent: Pseudotumor cerebri including papillary oedema in adolescents

Psychiatric disorders

Frequent: Depression, irritability, euphoria

Less frequent: Psychomotor hyperactivity, anxiety, Aggression

Skin and subcutaneous tissue disorders

Frequent: Allergic exanthema, petechiae, ecchymosis, delayed wound healing, contact dermatitis.

Less frequent: Ecchymosis

Vascular disorders

Less frequent: Increased risk of thrombosis, vasculitis (withdrawal syndrome after long-term therapy).

General disorders

Less frequent: Fatigue, malaise.

Occasionally side effects may occur which are typical for systemic glucocorticosteroids. These side effects depend on the dosage, the period of treatment, concomitant or previous treatment with other glucocorticosteroids and the individual sensitivity.

Clinical studies showed that the frequency of glucocorticosteroid associated side effects is lower with BUDENOFALK 3 mg CAPSULES (approx. by half) than with oral treatment of equivalent dosages of prednisolone.

An exacerbation or the reappearance of extraintestinal manifestations (especially affecting skin and joints) can occur on switching a patient from the systemically acting glucocorticosteroids to the locally acting budesonide.

Side effects in clinical studies with paediatric patients

Crohn's disease

In clinical trials with BUDENOFALK 3 mg CAPSULES in 82 paediatric patients with Crohn's disease adrenal suppression and headache were the most frequent undesirable effects. Side effects which are typical for steroids were reported as well as other rare reactions such as dizziness, nausea, vomiting, and hyperacusis.

Autoimmune hepatitis

*Safety data from the subset of a total of 42 paediatric patients in an autoimmune hepatitis clinical trial revealed that undesirable effects reported were not different and not more frequent compared to the adult population in this study (see also **section 5.1**).*

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. Healthcare professionals 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

Adverse drug reaction may be reported to Cipla via email address drugsafetysa@cipla.com.

4.9 Overdose

No specific antidote is available in cases of overdose. Treatment consists of supportive and symptomatic therapy. Serum electrolytes should be monitored**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 11.10 Medicines acting on the gastro-intestinal tract - Other

Budesonide is a topically acting glucocorticoid steroid used to treat inflammatory bowel disease. It is classified in the "corticosteroids acting locally" group of the Anatomical Therapeutic Chemical (ATC) classification system, ATC code A07EA06.

The exact mechanism of action of budesonide in the treatment of Crohn's disease is not fully understood. Data from clinical pharmacology studies and other controlled clinical trials strongly indicate that the mode of action of budesonide is predominantly based on a local action in the

gut. Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect. At doses clinically equivalent to systemically acting glucocorticosteroids, budesonide gives significantly less HPA axis suppression and has a lower impact on inflammatory markers.

Budesonide shows a dose-dependent influence on cortisol plasma levels which is at the recommended dose of 3 x 3 mg budesonide/day significantly smaller than that of clinically equivalent effective doses of systemic glucocorticosteroids.

Clinical efficacy and safety

Crohn's disease

Clinical study in adult patients with Crohn's disease

In a randomized, double-blind, double-dummy trial in patients with mild to moderate Crohn's disease (200 < CDAI < 400) affecting the terminal ileum and/or the ascending colon the efficacy of 9 mg budesonide in a single daily dose (9 mg OD) was non-inferior to 3 mg budesonide given three times daily (3 mg TID) in inducing remission over 8 weeks.

Paediatric population

Clinical studies in Crohn’s disease

Two randomised controlled studies with budesonide included patients in the age range of 8 to 19 years with mildly to moderately active Crohn’s disease (PCDAI [paediatric CD activity index] 12,5 to 40) with ileal, ileocolonic or isolated colonic inflammation. In one study, remission (PCDAI ≤ 10) was achieved with budesonide (both at week 4 and 12). A second study mean decrease of PCDAI at week 7 was defined as primary efficacy end point and secondary efficacy endpoints: improvement (defined as a decrease of PCDAI ≥ 10 points) was observed

Microscopic colitis

Clinical studies in induction of remission in collagenous colitis:

Efficacy and safety of budesonide for induction of remission in collagenous colitis were evaluated in two prospective double-blind (DB), randomized, placebo-controlled, multicentre studies in patients with active collagenous colitis.

In one study, the primary efficacy variable was the rate of patients in clinical remission, defined as ≤ 3 stools per day. Budesonide was safe and well tolerated. None of the adverse events in the budesonide group was considered drug related.

In another study, the primary efficacy variable was clinical response defined as a drop to ≤ 50 % of the disease activity at baseline with clinical disease activity defined as the numbers of stools during the last 7 days. Patients on budesonide achieved clinical response and it was safe and well tolerated. No serious adverse drug reactions occurred with budesonide.

Clinical study in maintenance of remission in collagenous colitis:

Clinical efficacy and safety of budesonide in the maintenance of remission in collagenous colitis were evaluated in a prospective double-blind (DB), randomized, placebo-controlled, multicentre study with patients with quiescent collagenous colitis. The primary endpoint was the proportion of patients in clinical remission over 52 weeks. Remission was defined as a mean of < 3 stools/day, thereof a mean of < 1 watery stool/day during the week prior to the final visit and with no relapse during the 1-year course. Relapse was defined as a mean of ≥ 3 stools/day thereof a mean of ≥ 1 watery stool/day during the previous week. In the final analysis, significantly more patients on budesonide reached the primary endpoint.

Clinical study in induction of remission in lymphocytic colitis:

Clinical efficacy and safety of budesonide in the induction of remission in lymphocytic colitis were evaluated in a prospective, double-blind (DB), double-dummy, randomized, placebo-

controlled, multicentre study with patients with active lymphocytic colitis. The primary endpoint was the rate of clinical remission, defined as a maximum of 21 stools, thereof not more than 6 watery stools in the last 7 days prior to the last visit. In the confirmatory analysis, significantly more patients on budesonide reached the primary endpoint at 8 weeks.

Autoimmune hepatitis

Clinical study in adult patients with autoimmune hepatitis:

In a prospective, double-blind, randomised, multicentre trial, patients with autoimmune hepatitis (AIH) without cirrhosis were treated with initial dose daily dose of 9 mg/d budesonide for up to 6 months and upon biochemical remission, the budesonide dose was reduced to 6 mg/d. The composite primary endpoint was complete biochemical remission (i.e. normal serum levels of aspartate- and alanine-aminotransferase) without occurrence of predefined steroid-specific side effects at 6 months. This primary endpoint was achieved in 47 % of the patients on budesonide.

Regarding secondary efficacy variables, at 6 months, complete biochemical remission occurred in more patients on budesonide. 72 % of the patients in the budesonide group did not develop steroid-specific side-effects. The Mean decrease in IgG and γ-globulin concentrations was reported.

Clinical study in paediatric patients with autoimmune hepatitis:

The safety and efficacy of budesonide in paediatric patients were studied.

The rate of complete responders (defined as biochemical response, i.e. normalisation of liver transaminases (ASAT, ALAT) and lack of steroid-specific side-effects) in patients aged ≤ 18 years was considerably lower compared to adult patients. There was no significant difference seen between the treatment groups.

5.2 Pharmacokinetic Properties

Absorption:

Budesonide gastro-resistant capsules which contain gastric juice resistant granules, have – due to the specific coating of the granules - a lag phase of 2 to 3 hours. In healthy volunteers, as well as in patients with Crohn's disease, mean maximal budesonide plasma concentrations of 1 to 2 ng/mL were seen at about 5 hours following an oral dose of budesonide capsules at a single dose of 3 mg, taken before meals. The maximal release therefore occurs in the terminal ileum and caecum, the main area of inflammation in Crohn's disease.

In ileostomy patients release of budesonide is comparable to healthy subjects or Crohn's disease patients. In ileostomy patients it was demonstrated that about 30 to 40 % of released budesonide is still found in the ileostomy bag, indicating that a substantial amount of budesonide will be transferred normally into the colon.
Concomitant intake of food may delay release of granules from stomach by 2 to 3 hours, prolonging the lag phase to about 4 to 6 hours, without change in absorption rates.

Distribution:

Budesonide has a high volume of distribution (approx. 3 l/kg). Plasma protein binding averages 85 to 90 %.

Biotransformation:

Budesonide undergoes extensive biotransformation in the liver (approx. 90 %) to metabolites with low glucocorticoid activity. The glucocorticosteroid activity of the main metabolites, 6β-hydroxybudesonide and 16α--hydroxyprednisolone, is less than 1 % of that of budesonide.

Elimination:

The average elimination half-life is about 3 to 4 hours. The systemic availability in healthy volunteers as well as in fasting patients with Crohn´s disease is about 9 to 13 %. Clearance of budesonide is about 10 to 15 l/min.

Budesonide is eliminated only in marginal if any amounts by the kidney.

Specific patient populations (liver diseases):

A relevant proportion of budesonide is metabolised in the liver. The systemic exposure of budesonide might be increased in patients with impaired hepatic function~~s~~ due to a decrease in budesonide metabolism by CYP3A4. This is dependent on the type and severity of liver disease.

5.3 Preclinical safety data

Preclinical data in acute, subchronic and chronic toxicological studies with budesonide showed atrophies of the thymus gland and adrenal cortex and a reduction of lymphocytes.

Budesonide had no mutagenic effects in a number of in vitro and in vivo tests.

A slightly increased number of basophilic hepatic foci were observed in chronic rat studies with budesonide, and in carcinogenicity studies an increased incidence of primary hepatocellular neoplasms, astrocytomas (in male rats) and mammary tumours (female rats) were observed. These tumours are probably due to the specific steroid receptor action, increased metabolic burden on the liver and anabolic effects. No similar effects have ever been observed in man for budesonide, neither in clinical trials nor from spontaneous reports.

In general, preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
In pregnant animals, budesonide has been shown to cause abnormalities of fetal development. But the relevance to man has not been established (see also **section 4.6.)**.

The active substance budesonide shows an environmental risk for the aquatic environment, especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The product contains the following inactive ingredients:

Ammonio methacrylate copolymer (type A) (Eudragit RL), ammonio methacrylate copolymer (type B) (Eudragit RS), lactose monohydrate, maize starch, methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L), methacrylic acid-methyl methacrylate copolymer (1:2) (Eudragit S), povidone K25, sucrose, talc, triethyl citrate

The capsule shell contains:

Black iron oxide (E 172), erythrosine (E 127), gelatin, purified water, red iron oxide (E 172), sodium laurilsulphate, titanium dioxide (E 171).

The product contains sugar:

Lactose monohydrate: 12 mg/capsule

Sucrose: 276 mg/capsule

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C

This medicine does not require any special storage conditions

6.5 Nature and contents of container

The product is packed in Aluminium/PVC/PVDC blister strips in sizes of 10, 20, 50, 90, 100 or 120 capsules packed in a cardboard carton.

6.6 Special precautions for disposal and other handling of the product

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

46/11.10/0842

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 July 2021

10. DATE OF REVISION OF THE TEXT

To be allocated