Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Budenofalk® 9mg gastro-resistant granules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 9mg budesonide.

Excipients with known effect: Each sachet contains 828mg sucrose, 36mg lactose monohydrate and 900mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant granules.
White to off-white granules and white to pale yellow powder with lemon flavour, filled into one sachet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon
Induction of remission in patients with active microscopic colitis in adults aged ≥ 18 years

4.2 Posology and method of administration

Posology

Crohn's disease and microscopic colitis

Adults aged > 18 years
The recommended daily dose is one sachet (containing gastro-resistant granules with 9mg budesonide) once daily in the morning about a half hour before breakfast.

Paediatric population
Budenofalk9mg gastro-resistant granules should not be taken by children and adolescents due to insufficient experience in this age group.

Patients with renal impairment
There are no specific dosage recommendations for patients with renal insufficiency (see section 5.2).

Patients with hepatic impairment
Since the information is limited in this patient-population a specific dose recommendation cannot be made (see sections 4.3, 4.4 and 5.2).

Method of administration
Oral use
The content of one sachet should be taken before breakfast. The granules should be placed on the tongue and swallowed whole, with plenty of liquid (e.g. a glass of water). The granules should not be chewed or crushed to avoid destruction of the gastro-resistant coating of the granules. Premature disintegration will affect drug disposition in an unpredictable fashion.

Duration of treatment
The duration of treatment should be limited to 8 weeks.

Termination of treatment
The treatment with Budenofalk9mg gastro-resistant granules should not be stopped abruptly. At the end of the treatment, Budenofalk 9mg gastro-resistant granules should be given in prolonged dosing intervals, i.e. every other day for up to two weeks. Afterwards treatment can be stopped.

4.3 Contraindications

Budenofalk 9mg gastro-resistant granules must not be used in patients with
– hypersensitivity to the active substance or to any of the excipients listed in section 6.1
– hepatic cirrhosis.

4.4 Special warnings and precautions for use

Treatment with Budenofalk 9mg gastro-resistant granules results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy. Transfer from other glucocorticosteroid therapy may result in symptoms relating to the change in systemic steroid levels.

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 glucocorticosteroids may have undesirable effects.

This medicine is not appropriate for patients suffering from Crohn's disease of the upper gastrointestinal tract.

Due to the preferential local mode of action of the compound beneficial effects for patients suffering from extraintestinal symptoms (e.g. of the eyes, skin, joints) cannot be expected.

Systemic effects of glucocorticosteroids 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 a wide range of psychiatric/behavioural effects (see section 4.8).

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 glucocorticosteroid 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 particular 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 glucocorticosteroids 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. Glucocorticosteroids 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.

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

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.

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.

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

Concomitant treatment with ketoconazole or other CYP3A4 inhibitors should be avoided (see section 4.5).

Budenofalk 9mg gastro-resistant granules contain lactose, sucrose and sorbitol. Patients with rare hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, total lactase deficiency or the congenital lactase deficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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 200mg once daily p.o. increased the plasma concentrations of budesonide (3mg 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 drugs such as carbamazepine and rifampicin, which induce CYP3A4, might reduce the systemic but also the local exposure of budesonide at the gut mucosa. An adjustment of the budesonide dose (using e.g. budesonide 3mg capsules) might be necessary

– *CYP3A4 substrates*
Compounds or drugs which are metabolized by CYP3A4 might be in competition with budesonide. This might 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 drug might be required.

Elevated plasma concentrations and enhanced effects of glucocorticosteroids 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 the 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 colestyramine, and with antacids cannot be ruled out. If given at the same time as Budenofalk 9mg gastro-resistant granules, 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Administration during pregnancy should be avoided unless there are compelling reasons for therapy with Budenofalk 9mg gastro-resistant granules. There are few data of pregnancy outcomes after oral administration of budesonide in humans. Although data on the use of inhaled budesonide in a large number of exposed pregnancies indicate no adverse effect, the maximal concentration of budesonide in plasma has to be expected to be higher in the treatment with Budenofalk 9mg gastro-resistant granules compared to inhaled budesonide. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause abnormalities of fetal development (see section 5.3). The relevance of this to man 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 Budenofalk 9mg gastro-resistant granule intake 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

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following frequency conventions are used in the evaluation of undesirable effects:

very common: (≥ 1/10)
common: (≥ 1/100 to < 1/10)
uncommon: (≥ 1/1,000 to < 1/100)
rare: (≥ 1/10,000 to < 1/1,000)
very rare: (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Frequency according to MedDRA convention	Adverse reaction
Metabolism and nutrition disorders	Common	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. amenorrhoea, hirsutism, impotence)
	Very rare	Growth retardation in children
Eye disorders	Rare	Glaucoma, cataract, blurred vision (see also section 4.4)
Gastrointestinal disorders	Common	Dyspepsia, abdominal pain
	Uncommon	Duodenal or gastric ulcer
	Rare	Pancreatitis
	Very rare	Constipation
Immune system disorders	Common	Increased risk of infection
Musculoskeletal and connective tissue disorders	Common	Muscle and joint pain, muscle weakness and twitching, osteoporosis
	Rare	Osteonecrosis
Nervous system disorders	Common	Headache
	Very rare	Pseudotumor cerebri including papilloedema in adolescents
Psychiatric disorders	Common	Depression, irritability, euphoria
	Uncommon	Psychomotor hyperactivity, anxiety
	Rare	Aggression
Skin and subcutaneous tissue disorders	Common	Allergic exanthema, petechiae, delayed wound healing, contact dermatitis
	Rare	Ecchymosis
Vascular disorders	Very rare	Increased risk of

		thrombosis, vasculitis (withdrawal syndrome after long-term therapy)
General disorders *and administration site conditions*	Very rare	Fatigue, malaise

Most of the adverse events mentioned in this SmPC can also be expected for treatments with other glucocorticosteroids.

Occasionally, adverse events may occur which are typical for systemic glucocorticosteroids. These adverse events 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 adverse events is lower with oral Budenofalk than with oral treatment of equivalent dosages of prednisolone.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system:
Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

To date, no cases of overdose with budesonide are known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids acting locally,
ATC code: A07EA06

The exact mechanism of budesonide in the treatment of inflammatory bowel diseases is not fully understood. Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of Budenofalk gastro-resistant granules 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.
Budenofalk gastro-resistant granules show a dose-dependent influence on cortisol plasma levels which is at the recommended dose of 9mg budesonide/day significantly smaller than that of clinically equivalent effective doses of systemic glucocorticosteroids.

Clinical efficacy and safety
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 9mg budesonide in a single daily dose (9mg OD) was compared to the treatment with 3mg budesonide given three times daily (3mg TID).
The primary efficacy endpoint was the proportion of patients in remission (CDAI<150) at week 8.

A total of 471 patients were included in the study (full analysis set, FAS), 439 patients were in the per protocol (PP) analysis set. There were no relevant differences in the baseline characteristics in both treatment groups. At the confirmatory analysis, 71.3% of the patients were in remission in the 9mg OD group and 75.1% in the 3mg TID group (PP) (p = 0.01975) demonstrating the non-inferiority of 9mg budesonide OD to 3mg budesonide TID.

No drug-related serious adverse events were reported.

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 with patients with active collagenous colitis.
In one study, 30 patients were randomized to a treatment with 9 mg budesonide per day, 25 patients to a treatment with 3 g mesalazine per day, and 37 to placebo. The primary efficacy variable was the rate of patients in clinical remission, defined as ≤ 3 stools per day. 80% of the patients treated with budesonide, 44% of the patients treated with mesalazine and 59.5% of the patients in the placebo-group reached the primary endpoint (budesonide vs. placebo = 0.072). According to another definition of clinical remission taking into account also the stool consistency, i. e. a mean of < 3 stools per day and a mean of < 1 watery stool per day in the last 7 days prior to the last administration of the study drug, 80% of the patients in the budesonide group, 32.0% of the patients in the mesalazine group and 37.8% of the patients in the placebo-group achieved remission (budesonide vs. placebo: $p < 0.0006$). Budesonide was safe and well tolerated. None of the adverse events in the budesonide group was considered drug related.
In another study 14 patients were randomized to a treatment with 9 mg budesonide per day and 14 were randomized to placebo. 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. 57.1% of patients in the budesonide group and 21.4% in the placebo-group achieved clinical response ($p = 0.05$). Budesonide was safe and well tolerated. No serious adverse drug reactions occurred in the budesonide group.

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.
57 patients were randomised (each 19 patients in the budesonide group, mesalazine-group and placebo-group) and took at least one dose of the study medication (budesonide: 9 mg OD; mesalazine: 3 g OD). The treatment duration was 8 weeks.
In the confirmatory analysis, significantly more patients in the budesonide group (78.9%) compared to patients in the placebo-group (42.1%) reached the primary endpoint, showing the superiority of budesonide over placebo ($p = 0.010$). Of the patients in the mesalazine group, 63.2% reached clinical remission ($p = 0.097$ compared to placebo).

5.2 Pharmacokinetic properties

Absorption
Due to the specific coating of the Budenofalk 9mg gastro-resistant granules there is a lag phase of 2-3 hours. In fasting healthy volunteers, mean peak plasma concentrations of budesonide were 2.2 ng/mL at about 6 hours following a single oral dose of 9mg budesonide gastro-resistant granules.

In a study with a single dose of budesonide 3mg gastro-resistant granules it was shown that concomitant intake of food may delay release of granules from stomach by about 2-3 hours, prolonging the lag phase to about 4-6 hours, without change in absorption rates.

Distribution
Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding is, on average, 85-90 %.

Biotransformation
Budesonide undergoes extensive biotransformation in the liver (approximately 90%) to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6ß-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide.

Elimination
The average elimination half-life is about 3-4 hours. The systemic availability in healthy volunteers as well as in fasting patients with inflammatory bowel diseases is about 9-13 %. Clearance of budesonide is about 10-15 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 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 especially of lymphocytes. These effects were less pronounced or at the same magnitude as observed with other glucocorticosteroids. Like with other glucocorticosteroids, and in dependence of the dose and duration and in dependence of the diseases these steroid effects might also be of relevance in man.

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 and anabolic effects on the liver, effects which are also known from other glucocorticosteroids in rat studies and therefore represent a class effect in this species.

Budesonide had no effect on fertility in rats. In pregnant animals, budesonide, like other glucocorticosteroids, has been shown to cause fetal death and abnormalities of fetal development (smaller litter size, intrauterine growth retardation of fetuses and skeletal abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The relevance of these findings to man has not been established (see also section 4.6.).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonio methacrylate copolymer (type A) (Eudragit RL),
ammonio methacrylate copolymer (type B) (Eudragit RS),
citric acid (for pH-adjustment),
lactose monohydrate,
lemon flavour,
magnesium stearate,
methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L 100),
methacrylic acid-methyl methacrylate copolymer (1:2) (Eudragit S 100),
povidone K25,
sucralose,
sugar spheres (consisting of maize starch and sucrose),
sorbitol (E420),
talc,
triethyl citrate,
xanthan gum.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyester/aluminium/polyethylene foil sachet

Pack sizes: 15, 20, 30, 50, 60 sachets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Dr. Falk Pharma GmbH
Leinenweberstrasse 5
79108 Freiburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0573/002/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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