Summary of Product Characteristics

1. Name of the medicinal product

Budeson 9 mg 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

Acute mild to moderate Crohn's disease with involvement of the ileum (twisted intestine) and/or ascending colon (part of large bowel).

Collagenous colitis.

4.2 Posology and method of administration

Posology

Crohn's disease and collagenous 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
Budeson 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 Budeson 9 mg Granules should not be stopped abruptly. At the end of the treatment, Budeson 9 mg 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

Budeson 9 mg 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 Budeson 9 mg 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).

Budeson 9 mg 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 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 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. Budeson 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 Budeson, 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 Budeson. 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 Budeson 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 Budeson 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

System organ class	Frequency according to MedDRA convention	Adverse reaction
	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 Budeson 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

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 Budeson 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. Budeson 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 study in 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 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.

5.2 Pharmacokinetic properties

Absorption
Due to the specific coating of the Budeson 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, 6β-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
Sugar spheres (consisting of sucrose and maize starch), Sorbitol, Talc; Methacrylic acid, methylmethacrylate copolymer (1:1) [Eudragit L100]; Methacrylic acid, methylmethacrylate copolymer (1:2) [Eudragit S100]; Lactose monohydrate, Citric acid anhydrous, Xanthan gum, Triethyl citrate, Lemon flavor; Ammonio methacrylate copolymer Type B [Eudragit RS]; Ammonio methacrylate copolymer Type A [Eudragit RL]; Magnesium stearate, Sucralose, Povidone K25.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
Sachet foil made of Polyester/aluminium/polyethylene
30 sachets.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Manufacturer

Dr. Falk Pharma GmbH, Freiburg, Germany.

8. Registration holder

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

Registration number: 157-65-34837

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