SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Budeson rectal foam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 1.2 g foam contains 2 mg of budesonide.

Excipients with known effect
One actuation of **Budeson rectal foam** contains 600.3 mg propylene glycol, 8.4 mg cetyl alcohol and 15.1 mg cetostearyl alcohol (component of emulsifying wax).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rectal foam, pressurised container
White to pale white, creamy firm foam

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of active ulcerative colitis that is limited to the rectum and the sigmoid colon.

4.2 Posology and method of administration

Posology

Adults aged > 18 years
One actuation of 2 mg budesonide daily.

Paediatric population
Budeson rectal foam should not be used in children due to insufficient experience in this age group.

Method of administration

Budeson rectal foam can be applied in the morning or evening.

The canister is first fitted with an applicator and then shaken for about 15 seconds before the applicator is inserted into the rectum as far as comfortable. Note that the dose is only sufficiently accurate when the pump dome is held downwards as vertically as possible. To administer a dose of **Budeson rectal foam**, the pump

dome is fully pushed down and very slowly released. Following the activation the applicator should be held in position for 10 - 15 seconds before being withdrawn from the rectum.

The best results are obtained when the intestine is evacuated prior to administration of Budeson rectal foam.

Duration of treatment

The attending physician determines the duration of use. An acute episode generally subsides after 6 to 8 weeks. **Budeson rectal foam** should not be used after this period of time.

4.3 Contraindications

Budeson rectal foam 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 rectal foam** results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy with systemically acting corticoids. Transfer from other glucocorticosteroid therapy may result in reappearance or recurrence of 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.

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 cholangitis (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 oral 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).

This medicinal product contains 600.3 mg propylene glycol in each actuation of **Budeson rectal foam**. Propylene glycol may cause skin irritation.

Cetyl alcohol and cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

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 200 mg once daily p.o. 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 administration 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 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.

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 rectal foam**. 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 rectal foam** 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 application of **Budeson rectal foam** 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; vision, blurred (see also section 4.4)
Gastrointestinal disorders	Common	Dyspepsia
	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	Common	Burning in the rectum and pain
	Very rare	Fatigue, malaise

The following adverse reactions were additionally reported in clinical studies with **Budeson rectal foam** (frequency: uncommon): increased appetite, increase in erythrocyte sedimentation rate, leucocytosis, nausea, abdominal pain, flatulence, paraesthesias in the abdominal region, anal fissure, aphthous stomatitis, frequent urge to defecate, rectal bleeding, increase in transaminases (GOT, GPT), increase in parameters of cholestasis (GGT,AP), increase in amylase, change in cortisol, urinary tract infection, dizziness, disturbances of smell, insomnia, increased sweating, asthenia, increase in body weight.

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.

Some of the adverse events were reported after long-term use of orally administered budesonide.

Due to its local action, the risk of adverse reactions of **Budeson rectal foam** is generally lower than when taking systemically acting glucocorticosteroids.

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: Intestinal anti-inflammatory agents, corticosteroids acting locally
ATC code: A07EA06

The exact mechanism of action of budesonide in the treatment of ulcerative colitis/procto-sigmoiditis is not fully understood. Data from clinical pharmacology studies and 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 a dosage of 2 mg budesonide, applied rectally, budesonide leads to practically no suppression of the hypothalamus-hypophysis-adrenal cortex axis.
Budeson rectal foam investigated up to the daily dosage of 4 mg budesonide showed virtually no influence on the plasma cortisol level.

5.2. Pharmacokinetic properties

Absorption:
After oral application the systemic availability of budesonide is about 10%. After rectal administration the areas under the concentration time curves are about 1.5-fold higher than in historical controls considering the identical oral budesonide dose. Peak levels are obtained after an average of 2-3 hours after administering **Budeson rectal foam**.

Distribution:
Budesonide has a high volume of distribution (about 3 l/kg). Plasma protein binding averages 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, 6 β-hydroxybudesonide and 16 α-hydroxyprednisolone, is less than 1 % of that of budesonide.

Elimination:
The average elimination half-life is about 3 - 4 hours. The mean clearance rate is about 10 - 15 l/min for budesonide, determined by HPLC-based methods.

Spread:
A scintigraphic investigation with technetium-marked **Budeson rectal foam** on patients with ulcerative colitis showed that the foam spreads out over the entire sigmoid.

Specific patient populations (liver diseases):
Dependent on the type and severity of liver diseases the metabolism of budesonide might be decreased.

5.3 Preclinical safety data

Preclinical investigations on dogs have shown that **Budeson rectal foam** is well tolerated locally.
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. 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 there was an increased incidence of primary hepatocellular neoplasms, astrocytomas (in male rats) and mammary tumours (female rats) observed. These tumours are probably due to the specific steroid receptor action, increased metabolic burden on the liver and anabolic effects, effects which are also known from other glucocorticosteroids in rat studies and therefore represent a class effect. 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, like other glucocorticosteroids, has been shown to cause abnormalities of foetal development, but the relevance to man has not been established (see also section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Purified water
Emulsifying wax (Polawax®)
Macrogol stearyl ether (Brij®76)
Cetyl Alcohol
Citric acid monohydrate
Disodium edetate

Propellant:
Propane
n-Butane
Isobutane

Nitrogen

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

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

After first opening: 4 weeks.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.

This is a pressurised container, containing inflammable propellant.
Do not expose to temperature higher than 50°C, protected from direct sunlight. Do not

pierce or burn even when empty.

6.5. Nature and contents of container

Aluminium pressurised container with metering valve together with 14 PVC applicators coated with white soft paraffin and liquid paraffin for administration of the foam and 14 plastic bags for hygienic disposal of the applicators.

Pack size:
Original pack with 1 pressurised container, contains at least 14 doses of 1.2 g rectal foam each.

6.6 Special precautions for disposal
No special requirements.

7 MANUFACTURER

Dr. Falk Pharma GmbH
Leinenweberstr. 5
79108 Freiburg Germany

8 REGISTRATION HOLDER
Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

9 Registration number: 173 96 36576 99.

This leaflet format has been determined by the Ministry of Health and its content has been checked and approved in September 2023.