SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Budeson® 4 mg suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 4 mg of budesonide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository.

White, torpedo-shaped suppositories (approximately 2 cm length) with a smooth surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of mild to moderate acute ulcerative colitis limited to the rectum (ulcerative proctitis) in adult patients.

4.2 Posology and method of administration

Posology

The recommended daily dose is 4 mg budesonide as one 4-mg-suppository.

Method of administration

For rectal administration only.

Budeson 4 mg suppositories should be administered at bedtime. If possible, the bowel should be emptied prior to administration of **Budeson 4 mg suppositories** in order to obtain the best results.

Duration of treatment

The duration of treatment is determined by the physician. An acute episode generally subsides after 6 to 8 weeks. **Budeson 4 mg suppositories** should not be used after this period of time.

Special populations

Renal impairment

There are currently no data available for patients with renal impairment. Because budesonide is excreted via the kidneys only to a minor extent, patients with mild to moderate impairment may be treated with the same doses as patients without renal impairment.

Even though the pharmacokinetics of budesonide are not expected to be altered in patients with renal impairment, in the absence of further data, caution should be exercised in the administration of the product to patients with severe renal impairment.

Hepatic impairment

Budeson 4 mg suppositories have not been studied in patients with hepatic impairment, therefore caution should be exercised in the administration of the product in these patients (see also sections 4.3, 4.4 and 5.2).

Elderly (>65 years)

No special dose adjustment is recommended. However, experience with the use of **Budeson 4 mg suppositories** in the elderly is limited.

Paediatric population

The safety and efficacy of **Budeson 4 mg suppositories** in children and adolescents under the age of 18 years have not been established. No data are available.

4.3 Contraindications

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

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. Such effects may include Cushing's syndrome, adrenal suppression, 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. Passive immunisation with varicella-zoster immunoglobulin (VZIG) is needed in 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. For **Budeson 4 mg suppositories**, no specific dose adjustment for patients with non-cirrhotic liver diseases or only slightly impaired liver function is necessary.

Patients with renal disorders

Even though the pharmacokinetics of budesonide are not expected to be altered in patients with renal impairment, in the absence of further data, caution should be exercised in the administration of the product to patients with severe renal impairment.

Visual disturbance

Visual disturbance has been 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.

Interference with serological testing

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

Elderly (>65 years)

It should be considered that side effects may occur more frequently in elderly patients. Therefore, elderly patients should be closely monitored for side effects.

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 and adrenal suppression is suspected, supplementary systemic glucocorticosteroid treatment is recommended.

Treatment with **Budeson 4 mg suppositories** results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy with systemically acting corticoids. Transfer from other glucocorticosteroid therapy may result in recurrence of symptoms relating to the change in systemic steroid levels.

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

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, which is a potential and known adverse reaction of glucocorticoids.

Saluretics

Concomitant use of glucocorticoids may result in enhanced potassium excretion and aggravated hypokalaemia.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Administration during pregnancy should be avoided unless there are compelling reasons for therapy with **Budeson 4 mg suppositories**. 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 4 mg suppositories** 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 administration of **Budeson 4 mg suppositories** 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

Budeson 4 mg suppositories have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Frequencies are defined as 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) or not known (cannot be estimated from the available data).

The following adverse drug reactions have been observed in clinical studies with **Budeson 4 mg suppositories**:

MedDRA system organ class	**Very common**	**Uncommon**
Endocrine disorders		Adrenal insufficiency
Nervous system disorders		Headache
Vascular disorders		Flushing
Gastrointestinal disorders		Abdominal pain, flatulence, pancreatitis
Skin and subcutaneous tissue disorders		Rash
Reproductive system and breast disorders		Menstrual disorder, irregular menstruation
Investigations	Cortisol decreased	

The following known adverse reaction of the therapeutic class (corticosteroids, budesonide) can also occur under **Budeson 4 mg suppositories** (frequency unknown):

MedDRA system organ class	**Adverse reaction**
Immune system disorders	Increased risk of infection
Endocrine disorders	Cushing's syndrome
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia
Psychiatric disorders	Depression, irritability, euphoria, psychomotor hyperactivity, anxiety, aggression
Eye disorders	Glaucoma, cataract, blurred vision (see also section 4.4)
Vascular disorders	Increased risk of thrombosis, vasculitis, hypertension
Gastrointestinal disorders	Dyspepsia, gastric and duodenal ulcers, constipation
Skin and subcutaneous tissue disorders	Allergic exanthema, petechiae, delayed wound healing, contact dermatitis, ecchymosis
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia, muscle weakness, muscle twitching, osteoporosis, osteonecrosis
General disorders	Malaise, fatigue

These adverse reactions are typical for systemic glucocorticosteroids. Their occurrence depends on the dosage, the period of treatment, concomitant or previous treatment with other glucocorticosteroids and the individual sensitivity.

Due to its local action, the risk of systemic adverse reactions of **Budeson 4 mg suppositories** is generally lower than when taking systemically acting glucocorticosteroids.

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

In case of a short-term overdose, no emergency medical treatment is required. There is no specific antidote. Subsequent treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, corticosteroids acting locally, ATC code: A07EA06

Mechanism of action

The exact mechanism of action of budesonide in the treatment of ulcerative colitis/proctitis 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.

Clinical efficacy

A randomised, double-blind, double-dummy phase III clinical study (BUS-4/UCA) compared rectal treatment with **Budeson 4 mg suppositories** (BUS group) vs. **Budeson rectal foam** 2 mg (BUF group) in the treatment of patients with mildly to moderately active ulcerative proctitis. 577 adult patients were randomised (1:1) and given either 4 mg budesonide once daily (OD) as a suppository or 2 mg budesonide OD as rectal foam for eight weeks. The co-primary efficacy endpoints were clinical remission (defined as modified UC-DAI subscores for stool frequency = 0 or 1 and for rectal bleeding = 0) and mucosal healing (defined as modified UC-DAI subscore for mucosal appearance = 0 or 1). In the per protocol analysis (PPS), 197 out of 250 patients (78.8%) applying BUS and 194 out of 261 patients (74.3%) applying BUF achieved clinical remission (full analysis set (FAS): 211 of 281 patients (75.1%) in the BUS group and 204 of 290 patients (70.3%) in the BUF group). The rate of patients with mucosal healing in the BUS group was 81.2% (PPS; 203 out of 250 patients) compared to 81.2% (PPS; 212 out of 261 patients) in the BUF group (FAS: 214 of 281 patients (76.2%) in the BUS group vs. 220 of 290 patients (75.9%) in the BUF group).

Compared to baseline, morning-cortisol levels at the end of treatment were statistically significantly reduced in both treatment groups of study BUS-4/UCA with a more pronounced decrease in the 4 mg BUS group than in the 2 mg BUF group. The clinical relevance of these findings has not been established.

Comparison between morning and evening application of the suppository resulted in a significant difference in favour of the evening application ($p = 0.03$) with a responder rate difference of 10.7 % for mucosal healing.

5.2 Pharmacokinetic properties

Absorption

Following rectal administration of **Budeson 4 mg suppositories** to healthy subjects, budesonide showed a median lag time of 0 h and a time to peak plasma concentration of 3.50 h. The mean peak plasma concentration (C_{max}) was 2.39 ng/mL and the area under the plasma-concentration-time curve ($AUC_{0-\infty}$) was 17.0 hr*ng/mL.

Repeated administration of **Budeson 4 mg suppositories** once daily over 6 days in healthy subjects did not lead to accumulation; the C_{max} was 2.65 ng/mL and the AUC in the dosing interval of 24 h ($AUC_{0-\tau}$) was 15.4 hr*ng/mL.

Distribution

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

Biotransformation

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

Elimination

The median elimination half-life after rectal administration of budesonide is 3.97 hours in healthy subjects. Budesonide has a high clearance rate of approximately 80 l/h.

Less than 1 % of the administered dose is cleared as intact budesonide via renal elimination.

An age-related decrease in elimination rate was observed after rectal administration of budesonide.

Hepatic impairment

A relevant proportion of budesonide is metabolised in the liver by CYP3A4. The systemic exposure of budesonide is considerably increased in patients with severely impaired hepatic function. No studies have been conducted with **Budeson 4 mg suppositories** in patients with impaired liver function.

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.

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 foetal death and abnormalities of foetal

development (smaller litter size, intrauterine growth retardation of foetuses and skeletal abnormalities). Some glucocorticoids have been reported to produce cleft palate in animals. The clinical relevance of these findings to man has not been established (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat [e.g. Witepsol® H15]

Ascorbyl palmitate

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

Do not store above 25 °C. Store protected from light, in the original packaging.

6.5 Nature and contents of container

White, peel-off PVC/LDPE or PVC/PVdC/LDPE strips.

Pack sizes of 12, 30 or 60 suppositories.

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 MANUFACTURER

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8 REGISTARTION HOLDER

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9 REGISTARTION NUMBER

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