SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Entocort® Enema.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

0.02 mg/ml budesonide (2 mg budesonide/100 ml).

Excipient(s) with known effect:

- Lactose anhydrous
- Lactose monohydrate
- Methyl-parahydroxybenzoate
- Propyl-parahydroxybenzoate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet and solution for rectal suspension.

Each Entocort enema consists of 2 components

- A 2.3 mg faintly yellow, circular biconvex tablet.
- A 115 ml clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis involving rectal and recto-sigmoid disease.

4.2 Posology and method of administration

Posology
Adults:
One Entocort Enema nightly for 4 weeks. Full effect is usually achieved within 2–4 weeks. If the patient is not in remission after 4 weeks, the treatment period may be prolonged to 8 weeks.

Paediatric population
Children: Not recommended.

Elderly
Dosage as for adults.

No dosage reduction is necessary in patients with reduced liver function.

Method of administration
The route of administration is rectal.

Instructions for correct use of Entocort enema.

Entocort enema consists of a dispersible tablet, a vehicle in a bottle and an individually packed nozzle for the application of the enema.

Note: it is important to instruct the patient

- To carefully read the instructions for use in the patient information leaflet which are packed together with each product.
- To reconstitute the enema immediately before use, put one dispersible tablet into the vehicle bottle, then shake the bottle vigorously for at least 15 seconds or until the tablet is completely dissolved.
- To administer in the evening before going to bed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Side effects typical of systemic corticosteroids may occur. Potential systemic effects include glaucoma.

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.

When patients are transferred from systemic glucocorticosteroid treatment with higher systemic effect to Entocort enema, they may have adrenocortical suppression. Therefore, monitoring of adrenocortical function may be considered in these patients and their dose of systemic steroid should be reduced cautiously.

Replacement of high systemic effect glucocorticosteroid treatment with Entocort enema sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic drug.

Reduced liver function affects the elimination of glucocorticosteroids, causing lower elimination rate and higher systemic exposure. Be aware of possible systemic side effects. The pharmacokinetics after oral ingestion of budesonide was affected by compromised liver function as evidenced by increased systemic availability in patients with moderately severe hepatic cirrhosis.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis (See section 4.8). Systemic effects of steroids 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).

Co-treatment with CYP3A inhibitors, including ketoconazole and 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. If this is not possible, the period between treatments should as long as possible, and a reduction of the budesonide dose could also be considered (see section 4.5).

Entocort enema contains the excipients lactose and methyl-, propyl-parahydroxybenzoate, therefore caution should be taken in patients with hypersensitivity to these excipients.
Some patients may feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of systemic glucocorticosteroids is sometimes necessary.

When Entocort Enema is used chronically in excessive doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear. However, the dosage form and the route of administration make any prolonged overdosage unlikely.

4.5 Interaction with other medicinal products and other forms of interaction

Raised plasma concentrations of and enhanced effects of corticosteroids have been reported in women also treated with oestrogens and contraceptive steroids. However, a low-dose combination oral contraceptive that more than doubled the plasma concentration of prednisolone, had no significant effect on the plasma concentration of oral budesonide.
The metabolism of budesonide is primarily mediated by CYP3A4, one of the cytochrome P450 enzymes.

Inhibitors of this enzyme, e.g. ketoconazole, itraconazole and HIV protease inhibitors, can therefore increase systemic exposure to budesonide several times (see Sections 4.4 and 5.2). Since there is no data to support a dosage recommendation, the combination should be avoided. If this is not possible, the period between treatments should as long as possible, and a reduction of the budesonide dose could also be considered. Other potent inhibitors of CYP3A4 are also likely to markedly increase plasma levels of budesonide. Inhibition by budesonide on other drugs metabolism via CYP3A4 is unlikely, since budesonide has low affinity to the enzyme.

Concomitant treatment with CYP3A4 inducers such as carbamazepine probably reduces budesonide exposure, which may require a dose increase.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The ability of corticosteroids to cross the placenta varies between individual drugs, however, in mice, budesonide and/or its metabolites have been shown to cross the placenta.

In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities in foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in humans. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

As with other drugs the administration of Entocort enema during pregnancy requires that the benefits for the mother are weighed against the risk for the foetus.

Breast-feeding

Budesonide is excreted in breast milk.

Maintenance treatment with inhaled budesonide (200 or 400 micrograms twice daily) in asthmatic nursing women results in negligible systemic exposure to budesonide in breast-fed infants.

In a pharmacokinetic study the estimated daily infant dose was 0.3% of the daily maternal dose for both dose levels, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma, assuming complete infant oral bioavailability. Budesonide concentrations in infant plasma samples were all less than the limit of quantification.

Based on data from inhaled budesonide and the fact that budesonide exhibits linear PK properties within the therapeutic dosage intervals after inhaled, oral and rectal administrations, at therapeutic doses of budesonide, exposure to the suckling child is anticipated to be low.

Infants of mothers taking higher than recommended doses of budesonide may have a degree of adrenal suppression.

These data support continued use of budesonide, oral and rectal administrations during breast-feeding.

4.7 Effects on ability to drive and use machines

Entocort Enema has no influence on the ability to drive and operate machinery.

4.8 Undesirable effects

The following definitions apply to the incidence 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).

Adverse drug reactions by frequency and system organ class (SOC)

SOC	Frequency	Reaction
Immune system disorders	Very rare	Anaphylactic reaction
	Unknown	Hypersensitivity reactions such as angioedema
Endocrine disorders	Rare	Signs or symptoms of systemic glucocorticosteroid effects, including hypofunction of the adrenal gland
Psychiatric disorders	Common	Depression
	Uncommon	Agitation, insomnia, anxiety,

	Rare	Aggression
Nervous system disorders	Uncommon	Psychomotor hyperactivity
Eye disorders	Rare	Glaucoma, cataract including subcapsular catarct, blurred vision (see also section 4.4)
Gastrointestinal disorders	Common	Gastrointestinal disturbances, e.g., flatulence, nausea, diarrhoea
	Uncommon	Duodenal or gastric ulcer
	Rare	Pancreatitis
Skin and subcutaneous tissue disorders	Common	Skin reactions (urticaria, exanthema)
	Rare	Ecchymosis
Musculoskeletal and connective tissue disorders	Rare	Osteonecrosis

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

Description of selected adverse events
In rare cases signs or symptoms of systemic glucocorticosteroid effects, including hypofunction of the adrenal gland, may occur with rectally administered glucocorticosteroids, probably depending on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual sensitivity.

Very rarely a wide range of psychiatric/ behavioural effects may occur, when systemic steroids are prescribed at high doses and for prolonged periods. (See section 4.4)

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 Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App.

4.9 Overdose

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Thus, acute overdosage with Entocort Enema, even in excessive doses, is not expected to be a clinical problem. In the event of acute overdosage, no specific antidote is available. If, by mistake, high doses of Entocort dispersible tablet have been taken orally, treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Budesonide is a glucocorticosteroid with a high local anti-inflammatory effect.

ATC Code A07E AO6.

Paediatric population
A 4-week single-blind, randomized, reference-controlled, parallel-group study compared the clinical efficacy and safety of glucocorticosteroid enemas in 47 children with ulcerative colitis. 23 children (range 7-15 years) were randomized and treated with Entocort Enema and 24 children (range 6 -15 years) with Pred-Clysma enema. The primary efficacy variable was remission, defined by endoscopic improvement and absence of clinical symptoms of ulcerative colitis. The remission rate after 4 weeks was 50% in the Entocort group and 71% in the Pred-Clysma group. The difference was not statistically significant. The primary safety variable was adrenal suppression, defined by changes in plasma cortisol levels after ACTH-stimulation. There was a statistically significant difference in the percentage of patients with normal adrenal function at week 4 (Entocort 73%, Pred-Clysma 33%). (Study LD-008-0003).

5.2 Pharmacokinetic properties

Budesonide undergoes an extensive degree (~90%) of biotransformation in the liver 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.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450.

At recommended doses, budesonide causes no or small suppression of plasma cortisol.

The mean maximal plasma concentration after rectal administration of 2 mg budesonide is 3 nmol/L (range 1-9 nmol/L), reached within 1.5 hours.

5.3 Preclinical safety data

Results from acute, subacute and chronic toxicity studies show that the systemic effects of budesonide, e.g. decreased body-weight gain and atrophy of lymphoid tissues and adrenal cortex, are less severe or similar to those observed after administration of other glucocorticosteroids.

Budesonide evaluated in six different test systems did not show any mutagenic or clastogenic effects.

An increased incidence of brain gliomas in male rats in a carcinogenicity study could not be verified in a repeat study, in which the incidence of gliomas did not differ

between any of the groups with active treatment (budesonide, prednisolone, triamcinolone acetonide) and the control groups.

Liver changes (primary hepatocellular neoplasms) found in male rats in the original carcinogenicity study were noted again in a repeat study with budesonide as well as with the reference glucocorticosteroids. These effects are most probably related to a receptor effect and thus represent a class-effect.

Available clinical experience shows that there are no indications that budesonide or other glucocorticosteroids induce brain gliomas or primary hepatocellular neoplasms in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet

Lactose anhydrous, riboflavine sodium phosphate (E101), lactose monohydrate, polyvidone, colloidal anhydrous silica and magnesium stearate.

Vehicle

Sodium chloride, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and water purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

Entocort Enema 0.02 mg/ml consists of 2 components: A dispersible tablet and a vehicle.

The primary package for the tablets is an aluminium blister package consisting of polyamide 25 μm/ Al ≥ 41 μm/ polyvinylchloride 60 μm/ A1 20 μm.

The primary package for the vehicle is a low density polyethylene (LDPE) bottle equipped with a high density polyethylene (HDPE) cap. .

Individually packaged nozzles (enema applicators) with non-return valves, both made of thermoplastic rubber.

Pack Size: each carton contains 7 tablets, 7 vehicle solutions, 7 nozzles (enema applicators), and 7 plastic bags to be used when giving the enema.

6.6 Special precautions for disposal

See section 4.2

7 MARKETING AUTHORISATION HOLDER

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