Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Entocort® CR 3 mg Gastro-resistant Capsule, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains budesonide 3 mg.
Excipient with known effect: not more than 295 mg sucrose
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant, prolonged release capsules, hard.

Hard gelatin capsules with an opaque, light grey body and opaque, pink cap marked **CIR 3mg** in black radial print

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn's disease:
Entocort CR Capsules are indicated for the induction of remission in patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon.

Active microscopic colitis:
Entocort CR Capsules are indicated for the induction of remission in patients with active microscopic colitis.
Entocort CR Capsules are indicated for the maintenance treatment of severe, recurrent microscopic colitis.

4.2 Posology and method of administration

Posology

Adults
Active Crohn's disease: The recommended daily dose for induction of remission is 9 mg once daily in the morning, for up to eight weeks. The full effect is usually achieved within 2 to 4 weeks of therapy.

When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy.

Entocort CR can be used for up to 3 months at the dose of 6 mg administered once daily in the morning. Long-term use is not recommended.

To replace prednisolone in steroid dependent patients, the recommended dose is 6 mg, administered once daily in the morning. When treatment with Entocort CR Capsules is initiated the prednisolone dose should be tapered.

To prevent recurrence after surgery in patients with high disease activity, the recommended dose is 6 mg, administered once daily in the morning. No benefit of Entocort has been shown in post surgical patients with obstructive fibrostenotic Crohn's disease.

Active Microscopic colitis:
Induction of remission: The recommended dose is 9 mg once daily in the morning (corresponding to 3 capsules), for up to eight weeks.

Maintenance of Microscopic colitis: Maintenance of remission therapy should be used only in patients who have already had a recurrence after discontinuation of induction therapy.
The recommended dose is 6 mg once daily in the morning (corresponding to 2 capsules) or the lowest effective dose.

When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy.

In line with general corticosteroid prescribing, the lowest effective dose should be given as clinically indicated.

Paediatric population
There is presently no experience with Entocort CR Capsules in children. Entocort is not recommended for use in children.

Older people
No special dose adjustment is recommended. However, experience with Entocort CR Capsules in older people is limited.

Method of administration
The capsules should be swallowed whole with water. The capsules must not be chewed.

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.

Use with caution in patients with bacterial, fungal or viral infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts or with a family history of diabetes or glaucoma or with any other condition where the use of glucocorticosteroids may have unwanted effects.

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 in their first-degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Treatment with Entocort CR Capsules results in lower systemic steroid levels than conventional oral glucocorticosteroid therapy. When patients are transferred from systemic glucocorticosteroid treatment with higher systemic effect to Entocort CR Capsules, 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 CR Capsules, sometimes unmasks allergies, e.g. rhinitis and eczema, which were previously controlled by the systemic drug.

Chicken pox and measles can have a more serious course in patients on oral glucocorticosteroids. Particular care should be taken to avoid exposure in patients who have not previously had these diseases. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

Glucocorticosteroids may cause suppression of the hypothalamus-pituitary-adrenal (HPA axis) and reduce the stress response. Where patients are subject to surgery or other stress situations, supplementary systemic glucocorticoid treatment is recommended.

As with all glucocorticosteroids the possibility of local or systemic infections should be borne in mind when using this product, particularly in view of the possible absence of systemic response thereto.

Reduced liver function may affect 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. The intravenous pharmacokinetics of budesonide however was similar in cirrhotic patients and in healthy subjects.

When treatment is to be discontinued, the dose should normally be reduced for the last 2 to 4 weeks of therapy. Some patients feel unwell in a non-specific way during the withdrawal phase, e.g. pain in muscles and joints. In some instances withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment. 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.

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 be as long as possible and a reduction of the budesonide dose could also be considered (see also section 4.5).

After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. As with other drugs primarily metabolised through CYP3A4, regular ingestion of grapefruit or its juice, should be avoided in connection with Entocort CR Capsules administration (other juices such as orange juice or apple juice do not inhibit CYP3A4). See also section 4.5.

When Entocort CR Capsules are used chronically in excessive doses, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may appear, and very rarely a wide range of psychiatric/behavioural effects may also occur (see section 4.8).

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Paediatric population
It is recommended that the height of children receiving prolonged treatment with glucocorticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated. The benefits of the glucocorticosteroid therapy and the possible risks of growth suppression must be carefully weighed. Long-term studies have not been performed in children treated with Entocort CR Capsules.

4.5 Interaction with other medicinal products and other forms of interaction

Although not studied, concomitant administration of colestyramine may reduce Entocort uptake, in common with other drugs.

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 oral prednisolone, had no significant effect on the plasma concentration of oral budesonide.

At recommended doses, omeprazole does not affect the pharmacokinetics of oral budesonide whereas cimetidine has a slight but clinically insignificant effect.

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. Inhibition of this enzyme by e.g. ketoconazole, itraconazole, HIV protease inhibitors and grapefruit juice can therefore increase the systemic exposure to budesonide several times, see section 4.4. 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 be as long as possible and a reduction of the budesonide dose could also be considered. Budesonide is unlikely to inhibit other drugs metabolised by CYP3A4 since it has low affinity to the enzyme.

Concomitant treatment with CYP3A4 inducers such as carbamazepine may reduce 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
In pregnant animals, administration of budesonide, like other glucocorticosteroids, is associated with abnormalities in foetal development. The relevance of this to humans has not been established. As with other drugs the administration of Entocort CR Capsules 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.

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 CR Capsules have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Table of 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); not known (cannot estimate from the available data).

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	Common	Cushingoid features
	Very rare	Growth retardation
Metabolism and nutrition disorders	Common	Hypokalemia
Psychiatric disorders	Common	Behavioural changes such as nervousness, insomnia, mood swings and depression
	Uncommon	Anxiety
	Rare	Aggression
Nervous system disorders	Uncommon	Tremor, psychomotor hyperactivity
Eye disorders	Rare	Glaucoma, cataract including subcapsular cataract, blurred vision (see also section 4.4)
Cardiac disorders	Common	Palpitations
Gastrointestinal disorders	Common	Dyspepsia
Skin and subcutaneous tissue disorders	Common	Skin reactions (urticaria, exanthema)
	Rare	Ecchymosis
Musculoskeletal and connective tissue disorders	Common	Muscle cramps

Reproductive system and breast disorders	Common	Menstrual disorders

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

Description of selected adverse events
Side effects typical of systemic corticosteroids (e.g. cushingoid features and growth retardation) may occur. These side effects are dependent on dose, treatment time, concomitant and previous corticosteroid intake, and individual sensitivity.

Clinical studies showed the frequency of steroid associated side effects for Entocort CR Capsules to be approximately half that of conventional prednisolone treatment, at equipotent doses. 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).

Paediatric population
Systemic and inhaled corticosteroids, including Entocort CR Capsules, may cause a reduction of growth velocity in paediatric patients. No long-term studies have been performed in paediatric patients treated with Entocort CR Capsules. Based on the available data from short-term studies (see section 5.1), the overall observed safety profile of Entocort CR Capsules in paediatric patients is consistent with the safety profile in adults.

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:
HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Reports of acute toxicity or death following overdosage of glucocorticosteroids are rare. Thus, acute overdosage with Entocort CR Capsules, even in excessive doses, is not expected to lead to an acute clinical crisis. In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

Chronic overdosage may lead to systemic corticosteroid effects, such as Cushingoid features. If such changes occur, the dose of Entocort CR Capsules should be gradually reduced until treatment is discontinued, in accordance with normal procedures for the discontinuation of prolonged oral glucocorticosteroid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids acting locally.

ATC Code: A07E A06.

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

The exact mechanism of budesonide in the treatment of Crohn’s disease is not fully understood.

Data from clinical pharmacology studies and controlled clinical trials strongly indicate that the mode of action of Entocort CR Capsules is based, at least partly, on a local action in the gut. At doses clinically equivalent to prednisolone, budesonide gives significantly less HPA axis suppression and has a lower impact on inflammatory markers.

At recommended doses, Entocort CR Capsules caused significantly less effect than prednisolone 20–40 mg daily on: morning plasma cortisols; 24 hour plasma cortisol (AUC 0-24h) and 24 hour urine cortisol levels.

ACTH tests have shown Entocort CR Capsules to have significantly less effect than prednisolone on adrenal functions.

In a study investigating bone mineral density during treatment with Entocort CR Capsules or prednisolone for up to two years, treatment with Entocort CR Capsules resulted in significantly less bone loss than prednisolone treatment in steroid naïve patients.

Microscopic colitis

Evidence for the indication microscopic (collagenous colitis and lymphocytic colitis) is presented below.

Collagenous colitis:

Two randomised, double-blind, placebo-controlled induction studies of six and eight weeks duration investigated the clinical and histological effect of Entocort 9 mg/day in the treatment of collagenous colitis. In the first study, 23 patients were randomised to Entocort 9 mg/day and 22 patients to placebo for 6 weeks. The rate of clinical remission was significantly higher ($p<0.001$) in the Entocort group than in the placebo group 86.9% vs. 13.6%. Histologic improvement was observed in 14 patients of the Entocort group (60.9%) and in one patient of the placebo group (4.5%; $p<0.001$). In the second study, 10 patients were randomised to Entocort for 8 weeks (9 mg/day 4 weeks, 6 mg/day 2 weeks, and 3 mg/day 2 weeks) and ten to placebo. All 10 patients receiving Entocort had a clinical response compared with two in the placebo group ($p<0.001$).

Two open-label studies (run-in phase of randomised, double-blind, placebo-controlled maintenance studies) investigated the efficacy of Entocort 9 mg/day during 6 weeks. In the first study, 46 patients (96%) achieved clinical remission within 2–30 (mean 6.4) days, with marked improvements in stool consistency. In the second study, of the 42 patients who commenced the study, 34 patients (81%) were in clinical remission (mean stool frequency of three or fewer per day) at week 6.

Lymphocytic colitis:

Evidence for this indication is limited to one randomised, double-blind placebo-controlled study in 15 lymphocytic colitis patients. Eleven subjects were treated with Entocort 9 mg/day and four patients received placebo for 8 weeks. A clinical response (defined as at least 50% improvement in the frequency of bowel movements) was seen in 25% of the placebo group vs. 91% in the Entocort group ($p=0.03$).

Paediatric population

HPA axis function. At recommended doses, Entocort CR Capsules cause significantly less effect than prednisolone 20-40 mg daily on morning plasma cortisol, on 24-hour plasma cortisol (AUC 0-24 h) and on 24-hour urine cortisol. Also ACTH tests have shown that Entocort CR Capsules, compared with prednisolone, have significantly less impact on the adrenal function. Children with Crohn's disease have a slightly higher systemic exposure and cortisol suppression than adults with Crohn's disease.

Long-term studies have not been performed in children treated with Entocort CR Capsules. In a study evaluating the effect of Entocort CR Capsules on cortisol suppression in 8 children (range 9–14 years) and 6 adults , the oral administration of 9 mg Entocort CR Capsules for 7 days induced a mean cortisol suppression (± SD) of 64% (±18%) in children and 50% (±27%) in adults with respect to baseline values. No clinically relevant findings in terms of safety have been reported. (Study 08-3044).

A study performed in children with mild to moderate Crohn's disease (CDAI ^{3} 200) compared the activity of Entocort CR Capsules at the dose of 9 mg once daily with that of prednisolone, administered at tapering doses, starting from 1 mg/kg. 22 patients were treated with Entocort CR Capsules and 26 patients were treated with the reference drug prednisolone. After 8 weeks of treatment, 70.8% of patients treated with prednisolone reached the endpoint (CDAI £ 150), as compared to 54.5% of subjects treated with Entocort CR Capsules, the difference was not statistically significant ($p = 0.13$). In the course of the study, adverse events were observed in 96% of patients treated with prednisolone and 91% of patients treated with Entocort

CR Capsules. The nature of these adverse events was similar in both study arms, but the incidence of glucocorticoid-related side-effects (such as acne and moon face) was lower in patients treated with Entocort CR Capsules. (Study SD-008-3037)

Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing ≤25 kg received 6 mg once daily for 8 weeks; patients weighing >25 kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean (±SD) PCDAI score from 19.1 (±10.1) to 9.1 (±8.5), indicating an improvement in disease activity; with an improvement in mean (±SD) IMPACT 3 score from 132.1 (±18.8) to 140.9 (±16.9). AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI ≤10). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

5.2 Pharmacokinetic properties

Absorption
After oral dosing of plain micronised compound, absorption is rapid and seems to be complete. A large proportion of the drug is absorbed from the ileum and ascending colon. Systemic availability in healthy subjects is approximately 9–12% for Entocort CR Capsules, similar to the systemic availability of plain micronised budesonide, indicating complete absorption. In patients with active Crohn's disease systemic availability is approximately 12–20%.

Distribution
Budesonide has a high volume of distribution (about 3 L/kg). Plasma protein binding averages 85–90%. In healthy volunteers mean maximal plasma concentrations of 5–10 nmol/L were seen at 3–5 hours following a single oral dose of Entocort CR Capsules 9 mg.

Biotransformation
Budesonide then undergoes extensive biotransformation in the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxy-prednisolone, is less than 1% of that of budesonide. The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450.

Elimination
Elimination is rate-limited by absorption. The average terminal half-life is 4 hours. Budesonide has a high systemic clearance (about 1.2 L/min).

Paediatric population
In a study comparing the pharmacokinetics of Entocort CR Capsules in 8 children (range 9–14 years) and 6 adults, Entocort CR Capules 9 mg for 7 days induced a systemic exposure (AUC) that was 17% higher in children than in adults, with maximum concentrations (C_{max}) 50% higher in children than in adults (mean AUC ± SD: children 41.3 nmol/L ± 21.2; adults 35.0 nmol/L ± 19.8. Mean C_{max} ± SD: children 5.99 nmo/L ± 3.45; adults 3.97 nmo/L ± 2.11.) (Study 08-3044).

5.3 Preclinical safety data

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

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 on 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 the repeat study with budesonide as well as 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.

The toxicity of Entocort CR Capsules, with focus on the gastro-intestinal tract, has been studied in cynomolgus monkeys in doses up to 5 mg/kg after repeated oral administration for up to 6 months. No effects were observed in the gastrointestinal tract, neither at gross pathology nor in the histopathological examination.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylcellulose
Tributyl acetylcitrate
Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent
Triethylcitrate
Simeticone (Antifoam M)
Polysorbate 80
Talc
Sugar spheres (consisting of sucrose and maizestarch)

Capsule shell:
Black iron oxide (E 172)
Titanium dioxide (E 171)
Gelatin
Sodium laurilsulfate
Colloidal anhydrous silica
Liquid Paraffin
Red iron oxide (E 172)
Yellow iron oxide (E 172)

Printing ink:
Black Iron oxide (E 172)
Shellac
Ammonium hydroxide
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original package. Keep the container tightly closed.

6.5 Nature and contents of container

White, polyethylene bottles of 100 capsules, having a tamper-evident, childproof polypropylene screw cap, with an integral desiccant.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
Warmbacher Strasse 80
DE- 79618 Rheinfelden
Germany

8 MARKETING AUTHORISATION NUMBER

PA2018/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 1996

Date of last renewal: 24 September 2006

10 DATE OF REVISION OF THE TEXT

January 2024