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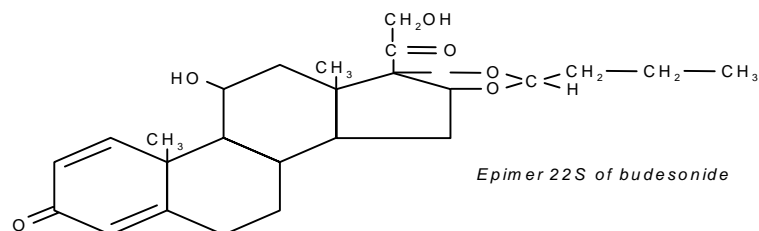
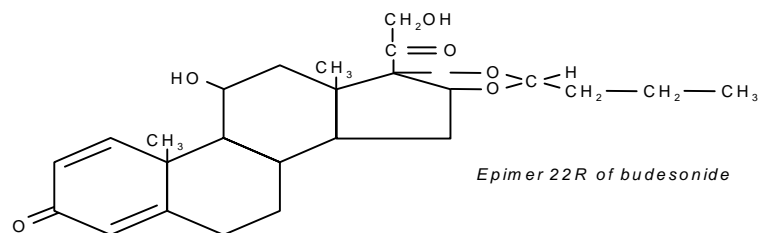
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ENTOCORT EC™ (budesonide) CAPSULES

Rx only

DESCRIPTION

Budesonide, the active ingredient of ENTOCORT EC™ capsules, is a synthetic corticosteroid. It is designated chemically as (RS)-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 5 is 1.6×10^3 ionic strength 0.01.

Each capsule contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide.

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CLINICAL PHARMACOLOGY

Budesonide has a high topical glucocorticosteroid (GCS) activity and a substantial first pass elimination. The formulation contains granules which are coated to protect dissolution in gastric juice, but which dissolve at pH >5.5, ie, normally when the granules reach the duodenum. Thereafter, a matrix of ethylcellulose with budesonide controls the release of the drug into the intestinal lumen in a time-dependent manner.

Pharmacokinetics

Absorption

The absorption of ENTOCORT EC seems to be complete, although C_{max} and T_{max} are variable. Time to peak concentration varies in individual patients between 30 and 600 minutes. Following oral administration of 9 mg of budesonide in healthy subjects, a peak plasma concentration of approximately 5 nmol/L is observed and the area under the plasma concentration time curve is approximately 30 nmol·hr/mL. The systemic availability after a single dose is higher in patients with Crohn's disease compared to healthy volunteers (21% vs 9%) but approaches that in healthy volunteers after repeated dosing.

Distribution

The mean volume of distribution (V_{ss}) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Metabolism

Following absorption, budesonide is subject to high first pass metabolism (80-90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6 β -hydroxy budesonide and 16 α -hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

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In vivo investigations with intravenous doses in healthy subjects are in agreement with the *in vitro* findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. Similarly, high plasma clearance values have been shown in patients with Crohn's disease. These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2.0 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^3H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6 β -hydroxy budesonide and 16 α -hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

Special Populations

No significant pharmacokinetic differences have been identified due to sex.

Hepatic Insufficiency

In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or V_{ss} are observed.

Renal Insufficiency

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (<1/100). Thus, patients with impaired renal function taking budesonide are not expected to have an increased risk of adverse effects.

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Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide severalfold. Co-administration of ketoconazole results in an eight-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels. Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (ie, ethinyl estradiol).

Since the dissolution of the coating of ENTOCORT EC is pH dependent (dissolves at pH >5.5), the release properties and uptake of the compound may be altered after treatment with drugs that change the gastrointestinal pH. However, the gastric acid inhibitory drug omeprazole, 20 mg qd, does not affect the absorption or pharmacokinetics of ENTOCORT EC. When an uncoated oral formulation of budesonide is co-administered with a daily dose of cimetidine 1 g, a slight increase in the budesonide peak plasma concentration and rate of absorption occurs, resulting in significant cortisol suppression.

Food Effects

A mean delay in time to peak concentration of 2.5 hours is observed with the intake of a high-fat meal, with no significant differences in AUC.

PHARMACODYNAMICS

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

Treatment with systemically active GCS is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to ACTH stimulation.

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Plasma cortisol suppression was compared following five days' administration of ENTOCORT EC capsules and prednisolone in a crossover study in healthy volunteers. The mean decrease in the integrated 0-24 hour plasma cortisol concentration was greater (78%) with prednisolone 20 mg/day compared to 45% with ENTOCORT EC 9 mg/day.

CLINICAL STUDIES

The safety and efficacy of ENTOCORT EC were evaluated in 994 patients with mild to moderate active Crohn's disease of the ileum and/or ascending colon in 5 randomized and double-blind studies. The study patients ranged in age from 17 to 85 (mean 35), 40% were male and 97% were white. Of the 651 patients treated with ENTOCORT EC, 17 (2.6%) were ≥65 years of age and none were >74 years of age. The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining efficacy in these 5 studies. The CDAI is a validated index based on subjective aspects rated by the patient (frequency of liquid or very soft stools, abdominal pain rating and general well-being) and objective observations (number of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal mass, body weight and hematocrit). Clinical improvement, defined as a CDAI score of ≤150 assessed after 8 weeks of treatment, was the primary efficacy variable in these 5 comparative efficacy studies of ENTOCORT EC capsules. Safety assessments in these studies included monitoring of adverse experiences. A checklist of potential symptoms of hypercorticism was used.

One study (Study 1) compared the safety and efficacy of ENTOCORT EC 9 mg qd in the morning to a comparator. At baseline, the median CDAI was 272. ENTOCORT EC 9 mg qd resulted in a significantly higher clinical improvement rate at Week 8 than the comparator (Table 1).

Table 1: Clinical Improvement Rates (CDAI ≤150) After 8 weeks of Treatment

Clinical Study	ENTOCORT EC 9 mg QD 4.5 mg BID	Comparator ^a	Placebo	Prednisolone
1	62/91 (69%)	37/83 (45%)		
2			13/64 (20%)	
3	38/79 (48%) 31/61 (51%) 41/78 (53%)		13/40 (33%)	
4	35/58 (60%) 25/60 (42%)			35/58 (60%)
5	45/86 (52%)			56/85 (65%)

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^aThis drug is not approved for the treatment of Crohn's disease in the United States

Two placebo-controlled clinical trials (Studies 2 and 3) were conducted. Study 2 involved 258 patients and tested the effects of grading doses of ENTOCORT EC (1.5 mg bid, 4.5 mg bid, or 7.5 mg bid) versus placebo. At baseline, the median CDAI was 290. The 3 mg per day dose level (data not shown) could not be differentiated from placebo. The 9 mg per day arm was statistically different from placebo (Table 1), while no additional benefit was seen when the daily ENTOCORT EC dose was increased to 15 mg per day (data not shown). In Study 3, the median CDAI at baseline was 263. Neither 9 mg qd nor 4.5 mg bid ENTOCORT EC dose levels was statistically different from placebo (Table 1).

Two clinical trials (Studies 4 and 5) compared ENTOCORT EC capsules with oral prednisolone (initial dose 40 mg per day). At baseline, the median CDAI was 277. Equal clinical improvement rates (60%) were seen in the ENTOCORT EC 9 mg qd and the prednisolone groups in Study 4. In Study 5, 13% fewer patients in the ENTOCORT EC group experienced clinical improvement than in the prednisolone group (no statistical difference) (Table 1).

The proportion of patients with normal plasma cortisol values (≥ 150 nmol/L) was significantly higher in the ENTOCORT EC groups in both trials (60 to 66%) than in the prednisolone groups (26 to 28%) at Week 8.

INDICATIONS AND USAGE

ENTOCORT EC is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

CONTRAINDICATIONS

ENTOCORT EC is contraindicated in patients with known hypersensitivity to budesonide.

WARNINGS

Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since ENTOCORT EC is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.

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Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of systemic steroid should be reduced cautiously.

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Caution should be taken in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

Replacement of systemic glucocorticosteroids with ENTOCORT EC capsules may unmask allergies, eg, rhinitis and eczema, which were previously controlled by the systemic drug.

When ENTOCORT EC capsules are used chronically, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur.

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Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis.

Information for Patients

ENTOCORT EC capsules should be swallowed whole and NOT CHEWED OR BROKEN.

Patients should be advised to avoid the consumption of grapefruit juice for the duration of their ENTOCORT EC therapy.

Patients should be given the patient package insert for additional information.

Drug Interactions

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, etc.) is indicated, reduction of the budesonide dose should be considered. 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 being metabolized through CYP3A4, ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis).

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation (TK^{+/-}) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

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Pregnancy

Teratogenic Effects: Pregnancy Category C: As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

Glucocorticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. The amount of budesonide secreted in breast milk has not been determined.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of ENTOCORT EC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety of ENTOCORT EC was evaluated in 651 patients. They ranged in age from 17 to 74 (mean 35), 40% were male and 97% were white, 2.6% were ≥ 65 years of age. Five hundred and twenty patients were treated with ENTOCORT EC 9 mg (total daily dose). In general, ENTOCORT EC was well tolerated in these trials. The most common adverse events reported were headache, respiratory infection, nausea, and symptoms of hypercorticism. Clinical studies have shown that the frequency of glucocorticosteroid-associated adverse events was substantially reduced with ENTOCORT EC capsules compared with prednisolone at therapeutically equivalent doses. Adverse events occurring in $\geq 5\%$ of the patients are listed in Table 2:

Table 2: Adverse Events Occurring in $\geq 5\%$ of the Patients in any Treated Group

	ENTOCORT EC 9 mg n=520	Placebo n=107	Prednisolone 40 mg n=145	Comparator* n=88
Adverse Event	Number (%)	Number (%)	Number (%)	Number (%)
Headache	107(21)	19(18)	31(21)	11(13)
Respiratory Infection	55(11)	7(7)	20(14)	5(6)
Nausea	57(11)	10(9)	18(12)	7(8)
Back Pain	36(7)	10(9)	17(12)	5(6)
Dyspepsia	31(6)	4(4)	17(12)	3(3)
Dizziness	38(7)	5(5)	18(12)	5(6)
Abdominal Pain	32(6)	18(17)	6(4)	10(11)
Flatulence	30(6)	6(6)	12(8)	5(6)
Vomiting	29(6)	6(6)	6(4)	6(7)
Fatigue	25(5)	8(7)	11(8)	0(0)
Pain	24(5)	8(7)	17(12)	2(2)

*This drug is not approved for the treatment of Crohn's disease in the United States.

Adverse events occurring in 520 patients treated with ENTOCORT EC 9 mg (total daily dose), with an incidence $<5\%$ and greater than placebo (n=107), are listed below by body system:

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Body as a Whole: *asthenia, C-Reactive protein increased, chest pain, dependent edema, face edema, flu-like disorder, malaise;*
Cardiovascular: *hypertension;* **Central and Peripheral Nervous System:** *hyperkinesia, paresthesia, tremor, vertigo;*
Gastrointestinal: *anus disorder, Crohn’s disease aggravated, enteritis, epigastric pain, gastrointestinal fistula, glossitis, hemorrhoids, intestinal obstruction, tongue edema, tooth disorder;*
Hearing and Vestibular: *Ear infection-not otherwise specified;*
Heart Rate and Rhythm: *palpitation, tachycardia;* **Metabolic and Nutritional:** *hypokalemia, weight increase;* **Musculoskeletal:** *arthritis aggravated, cramps, myalgia;* **Psychiatric:** *agitation, appetite increased, confusion, insomnia, nervousness, sleep disorder, somnolence;* **Resistance Mechanism:** *moniliasis;*
Reproductive, Female: *intermenstrual bleeding, menstrual disorder;* **Respiratory:** *bronchitis, dyspnea;* **Skin and Appendages:** *acne, alopecia, dermatitis, eczema, skin disorder, sweating increased;* **Urinary:** *dysuria, micturition frequency, nocturia;* **Vascular:** *flushing;* **Vision:** *eye abnormality, vision abnormal;* **White Blood Cell:** *leukocytosis*

Glucocorticosteroid Adverse Reactions

Table 3 displays the frequency and incidence of symptoms of hypercorticism by active questioning of patients in clinical trials.

Table 3: Summary and Incidence of Symptoms of Hypercorticism

	ENTOCORT EC 9 mg n=427	Placebo n=107	Prednisolone Taper 40 mg n=145
Symptom	Number (%)	Number (%)	Number (%)
Acne	63(15)	14(13)	33(23) *
Bruising Easily	63(15)	12(11)	13(9)
Moon Face	46(11)	4(4)	53(37) *
Swollen Ankles	32(7)	6(6)	13(9)
Hirsutism ^a	22(5)	2(2)	5(3)
Buffalo Hump	6(1)	2(2)	5(3)
Skin Striae	4(1)	2(2)	0(0)

^a Adverse event dictionary included term hair growth increased, local and hair growth increased, general.

*Statistically significantly different from ENTOCORT EC 9 mg

In addition to the symptoms in Table 3, three cases of benign intracranial hypertension have been reported in patients treated

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with budesonide from post-marketing surveillance. A cause and effect relationship has not been established.

CLINICAL LABORATORY TEST FINDINGS

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to ENTOCORT EC, were reported in $\geq 1\%$ of patients: hypokalemia, leukocytosis, anemia, hematuria, pyuria, erythrocyte sedimentation rate increased, alkaline phosphatase increased, atypical neutrophils, C-reactive protein increased, and adrenal insufficiency.

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily.

Single oral doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

DOSAGE AND ADMINISTRATION

The recommended adult dosage for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to 8 weeks. Safety and efficacy of ENTOCORT EC in the treatment of active Crohn's Disease have not been established beyond 8 weeks.

For recurring episodes of active Crohn's Disease, a repeat 8 week course of ENTOCORT EC can be given.

Treatment with ENTOCORT EC capsules can be tapered to 6 mg daily for 2 weeks prior to complete cessation.

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Patients with mild to moderate active Crohn's disease involving the ileum and/or ascending colon have been switched from oral prednisolone to ENTOCORT EC with no reported episodes of adrenal insufficiency. Since prednisolone should not be stopped abruptly, tapering should begin concomitantly with initiating ENTOCORT EC treatment.

Hepatic Insufficiency: Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Reducing the dose of ENTOCORT EC capsules should be considered in these patients.

CYP3A4 inhibitors: If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Reduction in the dose of ENTOCORT EC capsules should be considered.

ENTOCORT EC capsules should be swallowed whole and not chewed or broken.

HOW SUPPLIED

ENTOCORT EC 3 mg capsules are hard gelatin capsules with an opaque light grey body and an opaque pink cap, coded with CIR and 3 mg on the capsule.

They are supplied as follows:

NDC 0186-0702-10 Bottles of 100

Storage

Store at 25°C (77°F); excursions permitted to 15-30° (59-86°F) [See USP Controlled Room Temperature].

Keep container tightly closed.

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