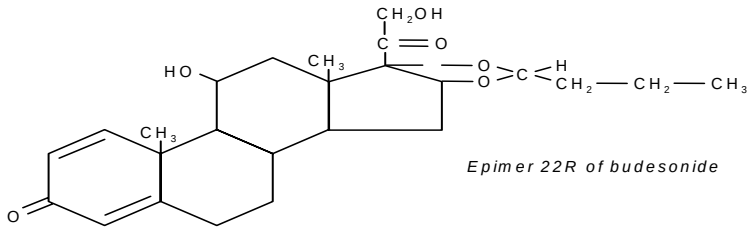
30029-XX

Entocort® EC
(budesonide) Capsules

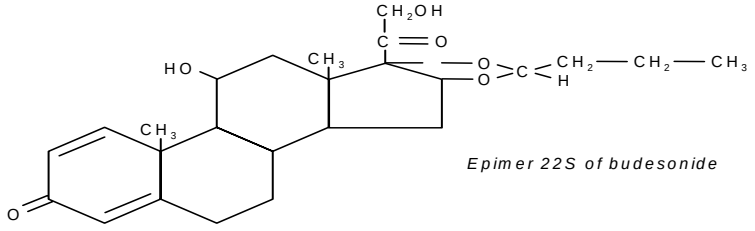
Rx only

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 $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Epimer 22R of budesonide



Epimer 22S of budesonide

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.

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/L. 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, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

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 [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-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.

Drug-Drug Interactions
Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several fold. 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.

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

*This 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 graded 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 ($\geq$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.

The efficacy and safety of ENTOCORT EC for maintenance of clinical remission were evaluated in four double-blind, placebo-controlled, 12-month trials in which 380 patients were randomized and treated once daily with 3 mg or 6 mg ENTOCORT EC or placebo. Patients ranged in age from 18 to 73 (mean 37) years. Sixty percent of the patients were female and 99% were Caucasian. The mean CDAI at entry was 96. Among the four clinical trials, approximately 75% of the patients enrolled had exclusively ileal disease. Colonoscopy was not performed following treatment. ENTOCORT EC 6 mg/day prolonged the time to relapse, defined as an increase in CDAI of at least 60 units to a total score >150 or withdrawal due to disease deterioration. The median time to relapse in the pooled population of the 4 studies was 154 days for patients taking placebo, and 268 days for patients taking ENTOCORT EC 6 mg/day. ENTOCORT EC 6 mg/day reduced the proportion of patients with loss of symptom control relative to placebo in the pooled population for the 4 studies at 3 months (28% vs. 45% for placebo).

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 and

- the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

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.

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.

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 hepatocycte 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).

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

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum.[1] Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant).

The recommended daily dose of ENTOCORT EC capsules is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 μg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for a 800 μg daily

dose of inhaled budesonide at steady state in the above inhalation study.

Since there are no data from controlled trials on the use of ENTOCORT EC by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from ENTOCORT EC, a decision should be made whether to discontinue nursing or to discontinue ENTOCORT EC, taking into account the clinical importance of ENTOCORT EC to the mother.

Budesonide, like other corticosteroids, is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of ENTOCORT EC, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation.

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ENTOCORT EC was evaluated in 651 patients in five short-term, active disease state studies. 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 ≥ 5% of the patients are listed in Table 2:

Table 2: Adverse Events Occurring in ≥ 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.

The safety of ENTOCORT EC was evaluated in 233 patients in four long-term clinical trials (52 weeks). A total of 145 patients were treated with ENTOCORT EC 6 mg. A total of 8% of ENTOCORT EC patients discontinued treatment due to adverse events compared with 10% in the placebo group. The adverse event profile in long-term treatment of Crohn's disease was similar to that of short-term treatment with ENTOCORT EC 9 mg in active Crohn's disease.

In the long-term clinical trials, the following adverse events occurred in ≥ 5% of the 6 mg ENTOCORT EC patients and are not listed in Table 2 or by body system below: diarrhea (10%); sinusitis (8%); infection viral (6%); and arthralgia (5%).

Adverse events occurring in 520 patients treated with ENTOCORT EC 9 mg (total daily dose) in short-term, active disease state studies, with an incidence of <5% and greater than placebo (n=107) are listed below by body system:

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

For the 145 patients treated with ENTOCORT EC 6 mg (total daily dose) in long-term studies, the following adverse events that are not included in the list above occurred with an incidence <5% but >2% and greater than for placebo: abscess, amnesia, dizziness, fever, pharynx disorder, purpura, rhinitis, and urinary tract infection.

Glucocorticosteroid Adverse Reactions

Table 3 displays the frequency and incidence of signs/symptoms of hypercorticism by active questioning of patients in short-term clinical trials.

Table 3: Summary and Incidence of Signs/Symptoms of Hypercorticism in Short-Term Studies

	ENTOCORT EC 9 mg n=427	**Placebo n=107**	**Prednisolone Taper 40 mg n=145**
Signs/Symptom	**Number (%)**	**Number (%)**	**Number (%)**
Acne	63(15)	14(13)	33(23) *

	ENTOCORT EC 9 mg n=427	Placebo n=107	Prednisolone Taper 40 mg n=145
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†	22(5)	2(2)	5(3)
Buffalo Hump	6(1)	2(2)	5(3)
Skin Striae	4(1)	2(2)	0(0)

*Statistically significantly different from ENTOCORT EC 9 mg

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

Table 4 displays the frequency and incidence of signs/symptoms of hypercorticism by active questioning of patients in long-term clinical trials.

Table 4: Summary and Incidence of Signs/Symptoms of Hypercorticism in Long-Term Studies

	ENTOCORT EC 3 mg n=88	ENTOCORT EC 6 mg n=145	Placebo n=143
Signs/Symptom	**Number (%)**	**Number (%)**	**Number (%)**
Bruising Easily	4(5)	15(10)	5(4)
Acne	4(5)	14(10)	3(2)
Moon Face	3 (3)	6(4)	0
Hirsutism	2 (2)	5(3)	1(1)
Swollen Ankles	2 (2)	3(2)	3(2)
Buffalo Hump	1 (1)	1 (1)	0
Skin Striae	2 (2)	0	0

The incidence of signs/symptoms of hypercorticism as described above in long-term clinical trials was similar to that seen in the short-term clinical trials.

A randomized, open, parallel-group multicenter safety study specifically compared the effect of ENTOCORT EC (<9 mg/day) and prednisolone (<40 mg/day) on bone mineral density over 2 years when used at doses adjusted to disease severity. Bone mineral density decreased significantly less with ENTOCORT EC

than with prednisolone in steroid-naïve patients, whereas no difference could be detected between treatment groups for steroid-dependent patients and previous steroid users. The incidence of treatment-emergent symptoms of hypercorticism was significantly higher with prednisolone treatment.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ENTOCORT EC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Anaphylactic reactions; ***Nervous System Disorders:*** Benign intracranial hypertension.

CLINICAL LABORATORY TEST FINDINGS

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to ENTOCORT EC, were reported in ≥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. Repeated 8 week courses of ENTOCORT EC can be given for recurring episodes of active disease.

Following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI <150), ENTOCORT EC 6 mg is recommended once daily for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months an attempt to taper to complete cessation is recommended. Continued treatment with ENTOCORT EC 6 mg for more than 3 months has not been shown to provide substantial clinical benefit.

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 ENTOCORT EC 3 mg on the capsule.

They are supplied as follows:

NDC 65483-702-10 Bottles of 100

Storage

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

Keep container tightly closed.

REFERENCES

1. Fält A, Bengtsson T, Kennedy B, et al. Exposure of infants to budesonide through breast milk of asthmatic mothers. *J. Allergy Clin Immunol*. 2007;120(4):798-802.

Manufactured by:
AstraZeneca AB
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Distributed by:
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PATIENT INFORMATION

ENTOCORT EC (budesonide) Capsules

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ENTOCORT EC (EN-toe-cort EE-CEE), ask your health care provider (provider). Only your provider can determine if ENTOCORT EC is right for you.

What is ENTOCORT EC?
ENTOCORT EC is a medicine to treat mild to moderate Crohn's disease in many people. However, it does not work for everyone who takes it. ENTOCORT EC is a *nonsystemic* corticosteroid, which means it works mainly in one area of the body. The medicine in ENTOCORT EC is released in the intestine. Therefore, it controls the symptoms of Crohn's disease even though 90% of the drug does not go into the bloodstream. Because of this, it causes fewer severe side effects than other corticosteroids. (See the end of this Patient Information for information about Crohn's disease.)

Who should not take ENTOCORT EC?

Do not take ENTOCORT EC if:

- you have had an allergic reaction to ENTOCORT EC or any of its ingredients

To help your provider decide if ENTOCORT EC is right for you, tell your provider:

- if you had an allergic reaction to any medicine in the past
- the names of all the prescription and nonprescription medicines you now take. Be sure to tell your provider if you take ketoconazole, which can affect processing of ENTOCORT EC by the liver, steroids such as prednisone, or any other drug that suppresses your immune system
- if you are pregnant, think you may be pregnant, or plan to get pregnant. Your provider will talk about whether ENTOCORT EC is right for you
- if you are breast feeding, talk with your provider because ENTOCORT EC is carried in human milk and it may

harm the baby. Your provider should tell you whether you should stop breast feeding to take ENTOCORT EC or should use another treatment.

- if you ever had liver problems. Liver problems affect the amount of ENTOCORT EC that stays in your system, and dosage may need to be changed
- if you are about to have surgery for any reason. Your dosage may need to be changed
- if you have chicken pox or measles, or any other condition that suppresses the immune system
- if you or anyone in your family has had diabetes or glaucoma
- if you ever had tuberculosis, high blood pressure, osteoporosis, ulcers, or cataracts.

How should I take ENTOCORT EC?

Take ENTOCORT EC in the morning. Swallow each ENTOCORT EC capsule whole. **Do not open, chew, or crush ENTOCORT EC capsules**. Your provider will tell you how long to take ENTOCORT EC.

What should I avoid while taking ENTOCORT EC?

Patients who take medicines that suppress the immune system, such as ENTOCORT EC, are more likely to get infections. Avoid people with infections. Also, if you never had chicken pox or measles, be careful to avoid people with these conditions. These conditions can be more serious if you get them while taking ENTOCORT EC.

While you are taking ENTOCORT EC, do not drink grapefruit juice regularly. Grapefruit juice can increase the amount of ENTOCORT EC in your blood. Other juices, like orange juice or apple juice, do not have this effect.

What are the side effects of ENTOCORT EC?

The most common side effects of ENTOCORT EC are headache, infection in your air passages (respiratory infection), nausea, and symptoms of hypercorticism (too much steroids in your body).

These symptoms include an increase in the size of the face and neck, acne, and bruising. Most symptoms of too much steroids in your body occur less often with ENTOCORT EC than with other steroids.

Call your provider right away if you notice itching, skin rash, fever, swelling of your face and neck, or trouble breathing while you are taking ENTOCORT EC. These may be signs that you are allergic to the medicine and you may need emergency medical help.

Switching from a systemic medicine, like prednisone, to a nonsystemic medicine, such as ENTOCORT EC, can cause allergies controlled by the systemic medicine to come back. These allergies may include eczema (a skin disease) or rhinitis (inflammation inside the nose).

Call your provider if:

- your Crohn's disease symptoms worsen during treatment
- you notice any side effects or any other symptoms that concern you

These are not all the possible side effects of ENTOCORT EC. Ask your provider or pharmacist for a complete listing of all possible side effects of ENTOCORT EC.

What is Crohn's disease?

Crohn's disease is an inflammatory bowel disease. The inflammation caused by Crohn's disease is usually found in a part of the small intestine called the ileum and in the large intestine (colon). It may also occur in any part of the gastrointestinal tract (digestive system) from the mouth to the anus (rectum). The cause of Crohn's disease is not yet known.

There are many symptoms of Crohn's disease. These include diarrhea, crampy abdominal (stomach area) pain, fever, and sometimes bleeding from the rectum. Appetite loss followed by weight loss may occur. There may also be redness and soreness of the eyes, joint pain, and sores on the skin. These symptoms may range from mild to severe.

There is no cure yet for Crohn's disease. However, it is possible for the disease to quiet down (go into remission). During these periods of remission, there may be times when the symptoms get worse. In general, people with Crohn's disease are able to lead productive lives.

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use

ENTOCORT EC for a condition for which it was not prescribed. Do not give ENTOCORT EC to other people, even if they have the same symptoms you have. It may harm them. Keep ENTOCORT EC and all medicines out of the reach of children.

This leaflet summarizes the most important information about ENTOCORT EC. If you would like more information, talk with your provider. You can ask your pharmacist or provider for information about ENTOCORT EC that is written for health professionals. You can also visit the ENTOCORT EC Web site at (**www.EntocortEC.com**) or call the information center at AstraZeneca toll-free (**1-800-237-8898**).

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