ENTOCORT® EC

(budesonide)

Capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENTOCORT® EC safely and effectively. See full prescribing information for ENTOCORT EC.

ENTOCORT® EC (budesonide) capsules, for oral use

Initial US Approval: 1997

INDICATIONS AND USAGE

ENTOCORT EC is a glucocorticosteroid indicated for:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. (1.1)
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months. (1.2)

DOSAGE AND ADMINISTRATION

- Mild to moderate active Crohn's disease: 9 mg 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. (2.1)
- Maintenance of clinical remission of mild to moderate Crohn's disease: 6 mg once daily for up to 3 months. Continued treatment with ENTOCORT EC 6 mg for more than 3 months has not been shown to provide substantial clinical benefit. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 3 mg (3)

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in ENTOCORT EC. (4)

WARNINGS AND PRECAUTIONS

- Hypercorticism and adrenal suppression: Since ENTOCORT EC is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. (5.1)
- Transferring patients from systemic glucocorticosteroid therapy: Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, such as ENTOCORT EC. (5.2)
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are headache, respiratory infection, nausea, back pain, dyspepsia, dizziness, abdominal pain, flatulence, vomiting, fatigue, pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cytochrome P450 3A4 inhibitors (e.g., ketoconazole, grapefruit juice) should be avoided. May cause increased systemic corticosteroid effects. (2.3, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Hepatic Insufficiency: Monitor patients for signs and/or symptoms of hypercorticism. (5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: December 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Exhibit 1032

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mild to Moderate Active Crohn's Disease

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

1.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

ENTOCORT EC is indicated for 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.

2 DOSAGE AND ADMINISTRATION

2.1 Mild to Moderate Active Crohn's Disease

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 orally 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.

2.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

Following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI less than 150), ENTOCORT EC 6 mg orally 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.

2.3 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. Grapefruit juice, which is known to inhibit CYP3A4, should also be avoided when taking ENTOCORT EC. In these cases, reduction in the dose of ENTOCORT EC capsules should be considered [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

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.

4 CONTRAINDICATIONS

ENTOCORT EC is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of ENTOCORT EC. Anaphylactic reactions have occurred [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Suppression

When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. 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.

5.2 Transferring Patients from Systemic Glucocorticosteroid Therapy

Care is needed in patients who are transferred from glucocorticosteroid treatment with high systemic effects to corticosteroids with lower systemic availability, such as ENTOCORT EC, 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 glucocorticosteroid treatment with high systemic effects should be reduced cautiously.

5.3 Immunosuppression

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 prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered.

Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections.

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

5.4 Increased Systemic Glucocorticosteroid Susceptibility

Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis [*see Use in Specific Populations (8.6)*].

5.5 Other Glucocorticosteroid Effects

Caution should be taken in patients with 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.

6 ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression [*see Warnings and Precautions (5.1)*]
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy [*see Warnings and Precautions (5.2)*]
- Immunosuppression [*see Warnings and Precautions (5.3)*]
- Increased Systemic Glucocorticosteroid Susceptibility [*see Warnings and Precautions (5.4)*]
- Other Glucocorticosteroid Effects [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to 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 greater than or equal to 65 years of age. Five hundred and twenty patients were treated with ENTOCORT EC 9 mg (total daily dose). The most common adverse reactions reported were headache, respiratory infection, nausea, and symptoms of hypercorticism. Clinical studies have shown that the frequency of glucocorticosteroid-associated adverse reactions was substantially reduced with ENTOCORT EC capsules compared with prednisolone at therapeutically equivalent doses. Adverse reactions occurring in greater than or equal to 5% of the patients are listed in Table 1:

Table 1 Adverse Reactions Occurring in greater than or equal to 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 Reaction	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 reactions compared with 10% in the placebo group. The adverse reaction 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 reactions occurred in greater than or equal to 5% of the 6 mg ENTOCORT EC patients and are not listed in (Table 1) or by body system below: diarrhea (10%); sinusitis (8%); infection viral (6%); and arthralgia (5%).

Adverse reactions, occurring in patients treated with ENTOCORT EC 9 mg (total daily dose) in short-term active disease state studies and/or ENTOCORT EC 6 mg (total daily dose) long-term, with an incidence less than 5% and greater than placebo are listed below by system organ class:

Blood and lymphatic system disorders: leukocytosis

Cardiac disorders: palpitation, tachycardia,

Eye disorders: eye abnormality, vision abnormal

General disorders and administration site conditions: asthenia, chest pain, dependent edema, face edema, flu-like disorder, malaise, fever

Gastrointestinal disorders: anus disorder, Crohn's disease aggravated, enteritis, epigastric

pain, gastrointestinal fistula, glossitis, hemorrhoids, intestinal obstruction, tongue edema, tooth disorder

Infections and infestations: Ear infection-not otherwise specified, bronchitis, abscess, rhinitis, urinary tract infection, thrush

Investigations: c-reactive protein increased, weight increased

Metabolism and nutrition disorders: appetite increased, hypokalemia

Musculoskeletal and connective tissue disorders: arthritis, cramps, myalgia

Nervous system disorders: hyperkinesia, parasthesia, tremor, vertigo, dizziness, somnolence, amnesia

Psychiatric disorders: agitation, confusion, insomnia, nervousness, sleep disorder

Renal and urinary disorders: dysuria, micturition frequency, nocturia

Reproductive system and breast disorders: intermenstrual bleeding, menstrual disorder

Respiratory, thoracic and mediastinal disorders: dyspnea, pharynx disorder

Skin and subcutaneous tissue disorders: acne, alopecia, dermatitis, eczema, skin disorder, sweating increased, purpura

Vascular disorders: flushing, hypertension

Table 2 displays the frequency and incidence of signs/symptoms of hypercorticism by active questioning of patients in short-term clinical trials.

Table 2 Summary and Incidence of Signs/Symptoms of Hypercorticism in Short-Term Studies

Signs/Symptom	ENTOCORT EC 9 mg n=427 Number (%)	Placebo n=107 Number (%)	Prednisolone Taper 40 mg n=145 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†	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 reaction dictionary included term hair growth increased, local and hair growth increased, general.

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

Table 3 Summary and Incidence of Symptoms of Hypercorticism in Long-Term Studies

Signs/Symptom	ENTOCORT EC 3 mg n=88 Number (%)	ENTOCORT EC 6 mg n=145 Number (%)	Placebo n=143 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 (less than 9 mg per day) and prednisolone (less than 40 mg per 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 symptoms associated with hypercorticism was significantly higher with prednisolone treatment.

Clinical Laboratory Test Findings

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

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval 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

Psychiatric Disorders: Mood swings

7 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. Ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: 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.

8.3 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 per 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 (less than 0.02 nmol/L in four infants and less than 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 mg 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 mg 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 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Systemic and inhaled corticosteroids, including ENTOCORT EC, may cause a reduction of growth velocity in pediatric patients.

8.5 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.

8.6 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 [*see Warnings and Precautions (5.4)*].

10 OVERDOSAGE

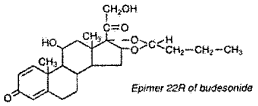
Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

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.

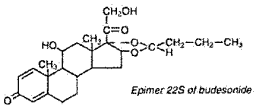
Single oral doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

11 DESCRIPTION

Budesonide, the active ingredient of ENTOCORT EC capsules, is a synthetic corticosteroid. Budesonide 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 for oral administration 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 greater than 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.

12.2 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 per day compared to 45% with ENTOCORT EC 9 mg per day.

12.3 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 (less than 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 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

Gender

No significant pharmacokinetic differences have been identified due to gender.

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 (less than 1/100).

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) [*see Drug Interactions (7)*].

Since the dissolution of the coating of ENTOCORT EC is pH dependent (dissolves at pH greater than 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 once daily 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.

13 NONCLINICAL TOXICOLOGY

13.1 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).

14 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 greater than or equal to 65 years of age and none were greater than 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 less than or equal to 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 reactions. A checklist of potential symptoms of hypercorticism was used.

One study (Study 1) compared the safety and efficacy of ENTOCORT EC 9 mg daily in the morning to a comparator. At baseline, the median CDAI was 272. ENTOCORT EC 9 mg daily resulted in a significantly higher clinical improvement rate at Week 8 than the comparator. See Table 4.

Table 4 Clinical Improvement Rates (CDAI less than or equal to 150) After 8 weeks of Treatment

Clinical Study	ENTOCORT EC 9 mg Daily	ENTOCORT EC 4.5 mg Twice Daily	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 twice daily, 4.5 mg twice daily, or 7.5 mg twice daily) 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 4), 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 daily nor 4.5 mg twice daily ENTOCORT EC dose levels was statistically different from placebo (Table 4).

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 daily 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 4).

The proportion of patients with normal plasma cortisol values (greater than 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 per day prolonged the time to relapse, defined as an increase in CDAI of at least 60 units to a total score greater than 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 per day. ENTOCORT EC 6 mg per 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

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 and are supplied as follows:

NDC 0186-0702-10 Bottles of 100

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

Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

"See FDA-Approved Patient Labeling (Patient Information)"

Patients being treated with ENTOCORT EC Capsules should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects. For proper use of ENTOCORT EC Capsules and to attain maximum improvement, the patient should read and follow the accompanying *FDA-Approved Patient Labeling.*

17.1 Hypercorticism and Adrenal Suppression

Patients should be advised that ENTOCORT EC Capsules may cause systemic glucocorticosteroid effects of hypercorticism and adrenal suppression. Patients should taper slowly from systemic glucocorticosteroids if transferring to ENTOCORT EC Capsules [*see Warnings and Precautions (5.1) and (5.2)*].

17.2 Immunosuppression

Patients who are on immunosuppressant doses of glucocorticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections [*see Warnings and Precautions (5.3)*].

17.3 How to Take ENTOCORT EC Capsules

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.

Distributed by:
AstraZeneca LP
Wilmington, DE 19850
Rev. 12/11 1600800 1/12

AstraZeneca

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.