

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021324Orig1s018

Trade Name: ENTROCORT EC

Generic or Proper Name: Budesonide

Sponsor: AstraZeneca Pharmaceuticals LP

Approval Date: January 18, 2019

Indication: ENTOCORT EC is indicated for:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older.
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults.

CENTER FOR DRUG EVALUATION AND RESEARCH

021324Orig1s018

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology / Virology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 021324/S018

SUPPLEMENT APPROVAL

Perrigo Pharma International DAC
Attention: Jocelyn Clark-Greuel MS, PhD, RAC, CRC
Senior Manager, Regulatory Affairs (US Agent)
Paddock Laboratories, LLC
3940 Quebec Avenue North
Minneapolis, MN 55427

Dear Jocelyn Clark-Greuel:

Please refer to your Supplemental New Drug Application (sNDA) dated December 14, 2017, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ENTOCORT EC (budesonide) extended-release capsules, 3 mg.

This Prior Approval supplemental new drug application provides for changes to the Prescribing Information and Patient Prescribing Information (PPI) labeling to:

- allow the capsules to be opened and administered by sprinkling on soft foods, for patients who are unable to swallow an intact capsule; and
- change the dosage form nomenclature from “capsules” to “extended-release capsules”

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, Instructions for Use, and Medication Guide), with the addition of any

labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

- 3075 – 1 An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.

We have reviewed your submission and conclude that the above commitment was fulfilled.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lawrence Allan, Regulatory Project Manager, at 240 – 402 – 2786.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Associate Director
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Prescribing Information
Patient Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA J LEE
01/18/2019 11:48:33 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021324Orig1s018

LABELING

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) extended-release capsules, for oral use
Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Dosage and Administration (2.1) 09/2018

INDICATIONS AND USAGE

ENTOCORT EC is a corticosteroid indicated for:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older. (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 in adults. (1.2)

DOSAGE AND ADMINISTRATION

Administration Instructions (2.1):

- Take once daily in the morning.
- Swallow whole. Do not chew or crush.
- For patients unable to swallow an intact capsule, open the capsules and empty the granules onto one tablespoonful of applesauce. Mix and consume the entire contents within 30 minutes. Do not chew or crush. Follow with 8 ounces of water.
- Avoid consumption of grapefruit juice for the duration of therapy.

Recommended Dosage:

Mild to moderate active Crohn's disease (2.2)

- Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses for recurring episodes of active disease.
- Pediatrics 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks.

Maintenance of clinical remission of mild to moderate Crohn's disease (2.3)

- Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.
- When switching from oral prednisolone, begin tapering prednisolone concomitantly with initiating ENTOCORT EC.

Hepatic Impairment:

- Consider reducing the dosage to 3 mg once daily in adult patients with moderate hepatic impairment (Child-Pugh Class B). (2.4, 5.1, 8.6)

DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules: 3 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Hypercorticism and Adrenal Axis Suppression:** Follow general warnings concerning corticosteroids; pediatrics and patients with hepatic impairment may be at increased risk. (2.4, 5.1, 8.4, 8.6)
- **Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids:** Taper slowly from corticosteroids with high systemic effects; monitor for withdrawal symptoms and unmasking of allergies (rhinitis, eczema). (5.2)
- **Increased Risk of Infection, including Serious and Fatal Chicken Pox and Measles:** Monitor patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. (5.3)
- **Other Corticosteroid Effects:** Monitor patients with concomitant conditions where corticosteroids may have unwanted effects (e.g., hypertension, diabetes mellitus). (5.4)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$) in adults are: headache, respiratory infection, nausea, back pain, dyspepsia, dizziness, abdominal pain, flatulence, vomiting, fatigue, and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

CYP3A4 Inhibitors (e.g., ketoconazole, grapefruit juice): Can increase systemic budesonide concentrations: avoid use. (2.1, 7.1)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Treatment of Mild to Moderate Active Crohn's Disease
- 1.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

2 DOSAGE AND ADMINISTRATION

- 2.1 Administration Instructions
- 2.2 Treatment of Mild to Moderate Active Crohn's Disease
- 2.3 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease
- 2.4 Dosage Adjustment in Adult Patients with Hepatic Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypercorticism and Adrenal Axis Suppression
- 5.2 Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids
- 5.3 Increased Risk of Infection
- 5.4 Other Corticosteroid Effects

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 CYP3A4 Inhibitors

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Treatment of Mild to Moderate Active Crohn's Disease
- 14.2 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of 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 in patients 8 years of age and older.

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 in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

- Take ENTOCORT EC once daily in the morning.
- Swallow ENTOCORT EC extended-release capsules whole. Do not chew or crush.
- For patients unable to swallow an intact capsule, ENTOCORT EC extended-release capsules can be opened and administered as follows:
 1. Place one tablespoonful of applesauce into a clean container (e.g., empty bowl). The applesauce used should not be hot and should be soft enough to be swallowed without chewing.
 2. Open the capsule(s).
 3. Carefully empty all the granules inside the capsule(s) on the applesauce.
 4. Mix the granules with the applesauce.
 5. Consume the entire contents within 30 minutes of mixing. Do not chew or crush the granules. Do not save the applesauce and granules for future use.
 6. Follow the applesauce and granules immediately with a glass (8 ounces) of cool water to ensure complete swallowing of the granules.
- Avoid consumption of grapefruit juice for the duration of ENTOCORT EC therapy [*see Drug Interactions (7.1)*].

2.2 Treatment of Mild to Moderate Active Crohn's Disease

The recommended dosage of ENTOCORT EC is:

Adults: 9 mg orally once daily for up to 8 weeks. Repeated 8 week courses of ENTOCORT EC can be given for recurring episodes of active disease.

Pediatric patients 8 to 17 years who weigh more than 25 kg: 9 mg orally once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks.

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

The recommended dosage in adults, following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI less than 150), is ENTOCORT EC 6 mg orally 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.

2.4 Dosage Adjustment in Adult Patients with Hepatic Impairment

Consider reducing the dosage of ENTOCORT EC to 3 mg once daily for adult patients with moderate hepatic impairment (Child-Pugh Class B). Avoid use in patients with severe hepatic impairment (Child-Pugh Class C) [*see Warnings and Precautions (5.1), Use in Specific Populations (8.6)*].

3 DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules: 3 mg hard gelatin capsules with an opaque light grey body and an opaque pink cap, coded with ENTOCORT EC 3 mg.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal axis suppression may occur. Corticosteroids 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 corticosteroid is recommended.

Since ENTOCORT EC contains a corticosteroid, general warnings concerning corticosteroids should be followed [*see Warnings and Precautions (5.2), (5.3), (5.4)*].

Pediatric patients with Crohn's disease have a slightly higher systemic exposure of budesonide and increased cortisol suppression than adults with Crohn's disease [see *Use in Specific Populations* (8.4), *Clinical Pharmacology* (12.2)]. Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism and consider reducing the dosage in patients with moderate hepatic impairment (Child-Pugh Class B) [see *Dosage and Administration* (2.4), *Use in Specific Populations* (8.6), *Clinical Pharmacology* (12.3)].

5.2 Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids

Monitor patients who are transferred from corticosteroid 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 axis suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of corticosteroid treatment with high systemic effects should be reduced cautiously.

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

5.3 Increased Risk of Infection

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 corticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure.

How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid 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.

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

5.4 Other Corticosteroid Effects

Monitor 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 corticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypercorticism and adrenal axis suppression [see Warnings and Precautions (5.1)]
- Symptoms of steroid withdrawal in those patients transferred from other systemic corticosteroids [see Warnings and Precautions (5.2)]
- Increased risk of infection [see Warnings and Precautions (5.3)]
- Other corticosteroid effects [see Warnings and Precautions (5.4)]

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.

Adults

The data described below reflect exposure to ENTOCORT EC in 520 patients with Crohn's disease, including 520 exposed to 9 mg per day (total daily dose) for 8 weeks and 145 exposed to 6 mg per day for one year in placebo controlled clinical trials. Of the 520 patients, 38% were males and the age range was 17 to 74 years.

Treatment of Mild to Moderate Active Crohn's Disease

The safety of ENTOCORT EC was evaluated in 651 adult patients in five clinical trials of 8 weeks duration in patients with active mild to moderate Crohn's disease. The most common adverse reactions, occurring in greater than or equal to 5% of the patients, are listed in Table 1.

Table 1 Common Adverse Reactions¹ in 8-Week Treatment Clinical Trials

Adverse Reaction	ENTOCORT		Prednisolone ²	
	EC 9 mg n=520	Placebo n=107	40 mg n=145	Comparator ³ n=88
	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)

¹. Occurring in greater than or equal to 5% of the patients in any treated group.

². Prednisolone tapering scheme: either 40 mg in week 1 to 2, thereafter tapering with 5 mg per week; or 40 mg in week 1 to 2, 30 mg in week 3 to 4, thereafter tapering with 5 mg per week.

³. This drug is not approved for the treatment of Crohn's disease in the United States.

The incidence of signs and symptoms of hypercorticism reported by active questioning of patients in 4 of the 5 short-term clinical trials are displayed in Table 2.

Table 2: Summary and Incidence of Signs/Symptoms of Hypercorticism in 8-Week Treatment Clinical Trials

Signs/ Symptom	ENTOCORT EC	Placebo	Prednisolone ¹
	9 mg n=427	n=107	40 mg n=145
	Number (%)	Number (%)	Number (%)
Total	145 (34%)	29 (27%)	69 (48%)
Acne	63 (15)	14 (13)	33 (23) ²
Bruising Easily	63 (15)	12 (11)	13 (9)
Moon Face	46 (11)	4 (4)	53 (37) ²
Swollen Ankles	32 (7)	6 (6)	13 (9)
Hirsutism ³	22 (5)	2 (2)	5 (3)
Buffalo Hump	6 (1)	2 (2)	5 (3)
Skin Striae	4 (1)	2 (2)	0 (0)

1. Prednisolone tapering scheme: either 40 mg in week 1-2, thereafter tapering with 5 mg/week; or 40 mg in week 1 to 2, 30 mg in week 3 to 4, thereafter tapering with 5 mg/week.

2. Statistically significantly different from ENTOCORT EC 9 mg

3. including hair growth increased, local and hair growth increased, general

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

The safety of ENTOCORT EC was evaluated in 233 adult patients in four long-term clinical trials (52 weeks) of maintenance of clinical remission in patients with mild to moderate Crohn's disease. A total of 145 patients were treated with ENTOCORT EC 6 mg once daily.

The adverse reaction profile of ENTOCORT EC 6 mg once daily in maintenance of Crohn's disease was similar to that of short-term treatment with ENTOCORT EC 9 mg once daily in active Crohn's disease. In the long-term clinical trials, the following adverse reactions occurred in greater than or equal to 5% and are not listed in Table 1: diarrhea (10%); sinusitis (8%); infection viral (6%); and arthralgia (5%).

Signs/symptoms of hypercorticism reported by active questioning of patients in the long-term maintenance clinical trials are displayed in Table 3.

Table 3: Summary and Incidence of Signs/Symptoms of Hypercorticism in Long-Term Clinical Trials

Signs/ Symptom	ENTOCORT EC	ENTOCORT EC	Placebo
	3 mg n=88	6 mg n=145	n=143
	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 maintenance clinical trials was similar to that seen in the short-term treatment clinical trials.

Less Common Adverse Reactions in Treatment and Maintenance Clinical Trials

Less common adverse reactions (less than 5%), occurring in adult patients treated with ENTOCORT EC 9 mg (total daily dose) in short-term treatment clinical studies and/or ENTOCORT EC 6 mg (total daily dose) in long-term maintenance clinical trials, with an incidence are listed below by system organ class:

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, 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: weight increased

Metabolism and nutrition disorders: appetite increased

Musculoskeletal and connective tissue disorders: arthritis, cramps, myalgia

Nervous system disorders: hyperkinesia, paresthesia, tremor, vertigo, 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: alopecia, dermatitis, eczema, skin disorder, sweating increased, purpura

Vascular disorders: flushing, hypertension

Bone Mineral Density

A randomized, open, parallel-group multicenter safety clinical trial 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.

Pediatrics -- Treatment of Mild to Moderate Active Crohn's Disease

Adverse reactions reported in pediatric patients 8 to 17 years of age, who weigh more than 25 kg, were similar to those reactions described above in adult patients.

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

7.1 CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with CYP3A4 inhibitors. Concomitant oral administration of a strong CYP3A4 inhibitor (ketoconazole) caused an eight-fold increase of the systemic exposure to oral budesonide. Inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine) can increase systemic budesonide concentrations [*see Clinical Pharmacology (12.3)*].

Grapefruit Juice

Avoid ingestion of grapefruit juice with budesonide. Intake of grapefruit juice which inhibits CYP3A4 activity with budesonide can increase the systemic exposure for budesonide [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published studies report on the use of budesonide in pregnant women; however, the data are insufficient to inform a drug-associated risk for major birth defects and miscarriage. There are clinical considerations [*see Clinical Considerations*]. In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.5 times or 0.05 times, respectively, the maximum recommended human dose, resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels [*see Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Some published epidemiological studies show an association of adverse pregnancy outcomes in women with Crohn's disease, including preterm birth and low birth weight infants, during

periods of increased disease activity (including increased stool frequency and abdominal pain). Pregnant women with Crohn's disease should be counseled regarding the importance of controlling disease.

Fetal/Neonatal adverse reactions

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly [*see Warnings and Precautions (5.1)*].

Data

Animal Data

Budesonide was teratogenic and embryolethal in rabbits and rats.

In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis from gestation days 6-15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis).

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses up to approximately 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis). Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.01 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).

In a peri- and post-natal development study, rats dosed subcutaneously with budesonide during the period of Day 15 post coitum to Day 21 postpartum, budesonide had no effects on delivery but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures 0.02 times the MRHD (on a mg/m² basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with oral budesonide, including ENTOCORT EC, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. One published study reports that budesonide is present in human milk

following maternal inhalation of budesonide [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENTOCORT EC and any potential adverse effects on the breastfed infant from ENTOCORT EC, or from the underlying maternal condition.

Data

One published study reports that budesonide is present in human milk following maternal inhalation of budesonide which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.4 and 0.5. Budesonide plasma concentrations were not detected and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide. The recommended daily dose of ENTOCORT EC is higher (up to 9 mg daily) compared with inhaled budesonide (up to 800 mcg daily) given to mothers in the above described 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 2.15 to 4.31 ng/mL which is up to 10 times higher than the 0.43 to 0.86 ng/mL for a 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. 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

The safety and effectiveness of ENTOCORT EC have been established in pediatric patients 8 to 17 years of age who weigh more than 25 kg for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. Use of ENTOCORT EC in this age group is supported by evidence from adequate and well controlled studies of ENTOCORT EC in adults, with additional data from 2 clinical studies in 149 pediatric patients treated up to 8 weeks and one pharmacokinetic study in 8 pediatric patients [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.1)*].

The observed safety profile of ENTOCORT EC in pediatric patients is consistent with its known safety profile in adults and no new safety concerns were identified [see *Adverse Reactions (6.1)*].

The safety and effectiveness of ENTOCORT EC have not been established in pediatric patients less than 8 years of age for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

The safety and effectiveness of ENTOCORT EC have not been established in pediatric patients for the maintenance of clinical remission of mild to moderate Crohn's disease. An open-label study to evaluate the safety and tolerability of ENTOCORT EC as maintenance treatment in

pediatric patients aged 5 to 17 years was conducted, and did not establish the safety and efficacy of maintenance of clinical remission.

Systemic corticosteroids, including ENTOCORT EC, may cause a reduction of growth velocity in pediatric patients. Pediatric patients with Crohn's disease have a 17% higher mean systemic exposure and cortisol suppression than adults with Crohn's disease [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)*].

8.5 Geriatric Use

Clinical studies of ENTOCORT EC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Of the 651 patients treated with ENTOCORT EC in clinical studies, 17 (3%) were greater than or equal to 65 years of age and none were greater than 74 years of age. 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 Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*]. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism and consider dosage reduction in patients with moderate hepatic impairment (Child-Pugh Class B) [*see Dosage and Administration (2.4)*]. No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A).

10 OVERDOSAGE

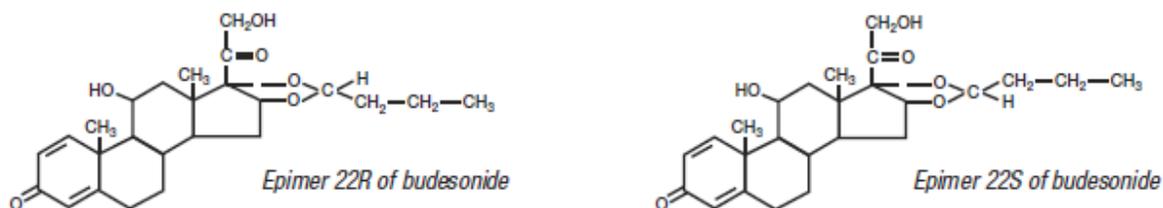
Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy.

If corticosteroids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism and adrenal axis suppression may occur. For chronic overdosage in the case 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 extended-release capsules, is a synthetic corticosteroid. Budesonide is designated chemically as (RS)-11 β , 16 α , 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.

Entocort EC is formulated as hard gelatin capsules filled with enteric-coated granules that dissolve at pH greater than 5.5. 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 is an anti-inflammatory corticosteroid and has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to glucocorticoid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

12.2 Pharmacodynamics

Treatment with glucocorticoids, including ENTOCORT EC is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. There was a positive correlation between the percent (%) reduction of AUC₀₋₂₄ of plasma cortisol and systemic exposure to budesonide both in pediatric and adult patients.

Adults

Plasma cortisol suppression was compared following five days' administration of ENTOCORT EC and prednisolone in a crossover study in healthy volunteers. The mean decrease in the area under the plasma cortisol concentration-time curve over 24 hour (AUC₀₋₂₄) was greater (78%) with prednisolone 20 mg per day compared to 45% with ENTOCORT EC 9 mg per day.

Pediatrics

The effect of budesonide on endogenous cortisol concentrations was compared between pediatrics (n=8, aged 9 to 14 years) and adults (n=6) with active Crohn's disease following administration of ENTOCORT EC 9 mg once daily for 7 days. Compared to baseline values before treatment, the mean decrease in the AUC₀₋₂₄ of cortisol was 64% (±18%) in pediatrics and 50% (±27%) in adults after ENTOCORT EC treatment [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)* and *Use in Specific Populations (8.4)*].

The responses to adrenocorticotropin challenge (i.e., ACTH stimulation test) was studied in pediatric patients aged 8 to 17 years, with mild to moderate active Crohn's disease in randomized, double-blind, active control study [see *Clinical Studies (14.1)*]. After 8 weeks of treatment with 9 mg once daily ENTOCORT EC or with prednisolone, administered at tapering doses starting from 1 mg/kg, the proportion of patients with normal response to the ACTH challenge was 6% in the budesonide group compared to none in the prednisolone group; the proportion of patients with morning p-cortisol of greater than 5 mcg/dL was 50% in the budesonide group compared to 22% in the prednisolone group. The mean morning p-cortisol was 6.3 mcg/dL in the budesonide group and 2.6 mcg/dL in the prednisolone group (Table 4).

Table 4. Proportion of Pediatric Patients 8 to 17 years old with Peak Endogenous Cortisol Levels (above 18 mcg/dL) after ACTH Stimulation and Normal Response* to ACTH Challenge Following Administration of ENTOCORT EC or Prednisolone for 8 weeks

	Budesonide	Prednisolone
Peak plasma cortisol above 18 mcg/dL		
At baseline	91% (20/22)	91% (21/23)
At week 8	25% (4/16)	0% (0/18)
Normal response* to ACTH challenge		
At baseline	73% (16/22)	78% (18/23)
At week 8	6% (1/16)	0% (0/18)

*The normal response to ACTH challenge included 3 criteria, as defined in the cosyntropin label: 1) morning cortisol level above 5 mcg/dL; 2) increase in cortisol level by at least 7 mcg/dL above the morning (pre-challenge) level following ACTH challenge; and cortisol level of above 18 mcg/dL following ACTH challenge. Cortisol concentration was measured at 30 min after intravenous or intramuscular injection of 0.25 mg cosyntropin at baseline and at week 8 after treatment.

12.3 Pharmacokinetics

Absorption

Following administration of ENTOCORT EC, the time to peak concentration varied in individual patients between 30 and 600 minutes. Mean oral bioavailability of budesonide ranged from 9% to 21% both in patients and in healthy subjects, demonstrating a high first-pass elimination of the drug.

Budesonide pharmacokinetics were dose-proportional following repeated administration in the dose range of 3 to 15 mg. No accumulation of budesonide was observed following repeated dosing.

Following oral administration of a single dose of 9 mg ENTOCORT EC in healthy subjects under fasting condition, the mean peak plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) for budesonide were 1.50 ± 0.79 ng/mL and 14.13 ± 7.33 ng•hr/mL, respectively. The time to peak concentration (T_{max}) varied between 2 and 8 hours with a median value of 3.5 hours. In a different study, following oral administration of 9 mg ENTOCORT EC for five days in healthy subjects, the mean C_{max} and the steady state AUC for budesonide were 2.28 ± 0.77 ng/mL and 15.93 ± 6.29 ng•hr/mL, respectively.

Following administration of 9 mg ENTOCORT EC once daily in patients with active Crohn's disease, the mean C_{max} and AUC were 1.72 ± 0.90 ng/mL and 15.07 ± 8.52 ng•hr/mL, respectively.

Concomitant administration of a high-fat meal delayed the T_{max} of budesonide from ENTOCORT EC by 2.3 hours but did not significantly affect the AUC in healthy subjects. The C_{max} and AUC to budesonide was similar when single dose of ENTOCORT EC (9 mg) were administered after opening capsule and sprinkling granules on applesauce versus as intact capsules in the fasted state (N=24) in healthy subjects.

Distribution

The mean volume of distribution (V_{ss}) of budesonide varied between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding was estimated to be 85% to 90% in the concentration range 0.43 to 99.02 ng/mL, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations was about 0.8.

Elimination

Budesonide had a plasma clearance, 0.9 to 1.8 L/min in healthy adults. Mean plasma clearance after intravenous administration of budesonide in patients with Crohn's disease was 1.0 L/min. These plasma clearance values approached the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug. The plasma elimination half-life, after

administration of intravenous doses ranged between 2 and 3.6 hours, and did not differ between healthy adults and patients with Crohn's disease.

Metabolism

Following absorption, budesonide is subject to high first pass metabolism (80% to 90%). *In vitro* experiments in human liver microsomes demonstrated 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 corticosteroid activity of these metabolites was negligible (less than 1/100) in relation to that of the parent compound. *In vivo* investigations with intravenous doses in healthy subjects were in agreement with the *in vitro* findings.

Excretion

Budesonide was 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 was 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 was detected in urine.

Specific Populations

Age: Pediatric Population (8 years and older)

The pharmacokinetics of budesonide were investigated in pediatric patients aged 9 to 14 years (n=8) after oral administration of ENTOCORT EC and intravenous administration of budesonide. Following administration of 9 mg ENTOCORT EC once daily for 7 days, the median time to peak plasma concentration of budesonide was 5 hours and the mean peak plasma concentration was 2.58 ± 1.51 ng/mL. The mean AUC was 17.78 ± 5.25 ng•hr/mL and 17% higher than that in adult patients with Crohn's disease in the same study. The mean absolute oral availability was 9.2% (3 to 17%; n=4) in pediatric patients.

After single dose administration of intravenous budesonide (n=4), the mean volume of distribution (V_{ss}) was 2.2 ± 0.4 L/kg and mean clearance was 0.81 ± 0.2 L/min. The mean elimination half-life was 1.9 hours in pediatric patients. The body-weight normalized clearance in pediatric patients was 20.5 mL/min/kg in comparison to 15.9 mL/min/kg in adult patients after intravenous administration [*see Warnings and Precautions (5.1), Use in Specific Population (8.4)*].

Hepatic Impairment

In patients with mild (Child-Pugh Class A, n=4) or moderate (Child-Pugh Class B, n=4) hepatic impairment, budesonide 4 mg was administered orally as a single dose. The patients with moderate hepatic impairment had a 3.5-fold higher AUC compared to the healthy subjects with

normal hepatic function while the patients with mild hepatic impairment had an approximately 1.4-fold higher AUC. The C_{max} values demonstrated similar increases [see *Dosage and Administration (2.4), Warnings and Precautions (5.1)*]. The increased systemic exposure in patients with mild hepatic impairment was not considered to be clinically relevant. Patients with severe liver impairment (Child-Pugh Class C) were not studied.

Drug Interaction Studies

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma concentrations of budesonide several-fold. Conversely, induction of CYP3A4 potentially could result in the lowering of budesonide plasma concentrations.

Effects of Other Drugs on Budesonide

Ketoconazole

In an open, non-randomized, cross-over study, 6 healthy subjects were given budesonide 10 mg as a single dose, either alone or concomitantly with the last ketoconazole dose of 3 days treatment with ketoconazole 100 mg twice daily. Co-administration of ketoconazole resulted in an eight-fold increase in AUC of budesonide, compared to budesonide alone [see *Drug Interactions (7.1)*].

Grapefruit Juice

In an open, randomized, cross-over study, 8 healthy subjects were given ENTOCORT EC 3 mg, either alone, or concomitantly with 600 mL concentrated grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), on the last of 4 daily administrations. Concomitant administration of grapefruit juice resulted in a 2-fold increase of the bioavailability of budesonide compared to budesonide alone [see *Drug Interactions (7.1)*].

Oral Contraceptives (CYP3A4 Substrates)

In a parallel study, the pharmacokinetics of budesonide were not significantly different between healthy female subjects who received oral contraceptives containing desogestrel 0.15 mg and ethinyl estradiol 30 µg and healthy female subjects who did not receive oral contraceptives. Budesonide 4.5 mg once daily (one-half the recommended dose) for one week did not affect the plasma concentrations of ethinyl estradiol, a CYP3A4 substrate. The effect of budesonide 9 mg once daily on the plasma concentrations of ethinyl estradiol was not studied.

Omeprazole

In a study in 11 healthy subjects, performed in a double-blind, randomized, placebo controlled manner, the effect of 5 to 6 days treatment with omeprazole 20 mg once daily on the pharmacokinetics of budesonide administered as ENTOCORT EC 9 mg as a single dose was

investigated. Omeprazole 20 mg once daily did not affect the absorption or pharmacokinetics of budesonide.

Cimetidine

In an open, non-randomized, cross-over study, the potential effect of cimetidine on the pharmacokinetics of budesonide was studied. Six healthy subjects received cimetidine 1 gram daily (200 mg with meals and 400 mg at night) for 2 separate 3-day periods. Budesonide 4 mg was administered either alone or on the last day of one of the cimetidine treatment periods. Co-administration of cimetidine resulted in a 52% and 31% increase in the budesonide peak plasma concentration and the AUC of budesonide, respectively.

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

14.1 Treatment of Mild to Moderate Active Crohn's Disease

Adults

The 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 of 8 weeks duration. The study patients ranged in age from 17 to 85 (mean 35), 40% were male and 97% were white. The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining efficacy in these 5 studies.¹ 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. 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 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 5.

Table 5: 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 Twice mg Daily	Comparator ³	Placebo	Prednisolone
1	62/91 (69%) ¹		37/83 (45%)		
2		31/61 (51%) ²		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%)

¹ p=0.0004 compared to comparator.

² p=0.001 compared to placebo.

³ 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 1.5 mg twice daily arm (data not shown) could not be differentiated from placebo. The 4.5 mg twice daily arm was statistically different from placebo (Table 5), while no additional benefit was seen when the daily ENTOCORT EC dose was increased to 15 mg per day (data not shown). Study 3 was a 3-armed parallel group study. The groups were treated with ENTOCORT EC 9

mg once daily, ENTOCORT EC 4.5 mg twice daily and placebo for 8 weeks, followed by a 2-week double-blind taper phase. The median CDAI at baseline was 263. Neither 9 mg daily nor 4.5 mg twice daily ENTOCORT EC dose levels were statistically different from placebo (Table 5). The recommended dosage of ENTOCORT EC for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in adults is 9 mg once daily in the morning for up to 8 weeks [*see Dosage and Administration (2.1)*].

Two clinical trials (Studies 4 and 5) compared ENTOCORT EC with oral prednisolone (initial dose 40 mg per day). Study 4 was a 3-armed parallel group study. The groups were treated with ENTOCORT EC 9 mg once daily, ENTOCORT EC 4.5 mg twice daily and prednisolone 40 mg (tapered dose) for 8 weeks, followed by a 4-week double blind taper phase. 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 5). The proportion of patients with normal plasma cortisol values (greater than 64.58 ng/mL) 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.

Pediatrics (8 to 17 Years of Age)

The effectiveness of ENTOCORT EC, in pediatric patients aged 8 to 17 years, who weigh more than 25 kg with mild to moderate active Crohn's disease (defined as Crohn's Disease Activity Index (CDAI) ≥ 200) involving the ileum and/or the ascending colon, was assessed in one randomized, double-blind, active control study. This study compared ENTOCORT EC 9 mg once daily, with prednisolone, administered at tapering doses starting from 1 mg/kg. Twenty-two (22) patients were treated with ENTOCORT EC capsules and 24 patients were treated with prednisolone. After 8 weeks of treatment, 55% (95% CI: 32%, 77%) of patients treated with ENTOCORT EC reached the endpoint (CDAI ≤ 150), as compared to 68% (95% CI: 47%, 89%) of patients treated with prednisolone. The average number of liquid or very soft stools per day (assessed over 7 days) decreased from 1.49 at baseline to 0.96 after treatment with ENTOCORT EC and 2.00 at baseline to 0.52 after treatment with prednisolone. The average daily abdominal pain rating (where 0=none, 1=mild, 2=moderate, and 3=severe) decreased from 1.49 at baseline to 0.54 after treatment with ENTOCORT EC and 1.64 at baseline to 0.38 after 8 weeks of treatment with prednisolone.

Use of ENTOCORT EC in this age group is supported by evidence from adequate and well-controlled studies of ENTOCORT EC in adults, and by safety and pharmacokinetic studies performed in pediatric patients.

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

Adults

The efficacy 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% versus 45% for placebo).

15 REFERENCES

1. Best WR, Beckett JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70(3): 439-444.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTOCORT EC 3 mg extended-release 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 0574-9850-10 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

Advise Patients to read the FDA-Approved patient labeling (Patient Information).

Hypercorticism and Adrenal Axis Suppression

Advise patients that ENTOCORT EC may cause hypercorticism and adrenal axis suppression and to follow a taper schedule, as instructed by their healthcare provider if transferring to ENTOCORT EC from systemic corticosteroids [see *Warnings and Precautions (5.1), (5.2)*].

Advise patients that replacement of systemic corticosteroids with ENTOCORT EC may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug.

Increased Risk of Infection

Advise patients to avoid exposure to people with chicken pox or measles and, if exposed, to consult their healthcare provider immediately. Inform patients that they are at increased risk of developing a variety of infections; including worsening of existing tuberculosis, fungal, bacterial, viral or parasitic infections or ocular herpes simplex and to contact their healthcare provider if they develop any symptoms of infection [*see Warnings and Precautions (5.3)*].

Pregnancy

Advise female patients that ENTOCORT EC may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Administration

- Take ENTOCORT EC once daily in the morning.
- Swallow ENTOCORT EC extended-release capsules whole. Do not chew or crush
- For patients unable to swallow an intact capsule, ENTOCORT EC extended-release capsules can be opened and administered as follows:
 1. Place one tablespoonful of applesauce into a clean container (e.g., empty bowl). The applesauce used should not be hot and should be soft enough to be swallowed without chewing.
 2. Open the capsule(s).
 3. Carefully empty all the granules inside the capsule(s) on the applesauce.
 4. Mix the granules with the applesauce.
 5. Consume the entire contents within 30 minutes of mixing. Do not chew or crush the granules. Do not save the applesauce and granules for future use.
 6. Follow the applesauce and granules immediately with a glass (8 ounces) of cool water to ensure complete swallowing of the granules.
- Avoid consumption of grapefruit juice for the duration of their ENTOCORT EC therapy [*see Drug Interactions (7.1)*].

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Manufactured for and Distributed by:



Allegan, MI 49010 Rev 11-17E 8Z200 RC JX

PATIENT INFORMATION
ENTOCORT® EC (EN-toe-cort EE CEE)
(budesonide)
extended-release capsules

Read this Patient Information before you start taking ENTOCORT EC and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is ENTOCORT EC?

ENTOCORT EC is a prescription corticosteroid medicine used to treat mild to moderate Crohn's disease that affects part of the small intestine (ileum) and part of the large intestine (ascending colon):

- in people 8 years of age and older with active Crohn's disease
- in adults to help keep symptoms from coming back for up to 3 months

It is not known if ENTOCORT EC is safe and effective in children under 8 years of age, or in children 8 to 17 years of age who weigh 55 pounds (25 kg) or less, for the treatment of mild to moderate active Crohn's disease that affects part of the small intestine (ileum) and part of the large intestine (ascending colon).

It is not known if ENTOCORT EC is safe and effective in children to help keep symptoms of mild to moderate Crohn's disease that affects part of the small intestine (ileum) and part of the large intestine (ascending colon) from coming back.

Who should not take ENTOCORT EC?

Do not take ENTOCORT EC if:

- you are allergic to budesonide or any of the ingredients in ENTOCORT EC. See the end of this leaflet for a complete list of ingredients in ENTOCORT EC.

Before you take ENTOCORT EC tell your healthcare provider if you have any other medical conditions including if you:

- have liver problems.
- are planning to have surgery.
- have chicken pox or measles or have recently been near anyone with chicken pox or measles.
- have an infection.
- have diabetes or glaucoma or have a family history of diabetes or glaucoma.
- have cataracts.
- have or had tuberculosis.
- have high blood pressure (hypertension).
- have decreased bone mineral density (osteoporosis).
- have stomach ulcers.
- are pregnant or plan to become pregnant. ENTOCORT EC may harm your unborn baby. Talk to your healthcare provider about the possible risk to your unborn baby if you take ENTOCORT EC when you are pregnant. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during your treatment with ENTOCORT EC.
- are breastfeeding or plan to breastfeed. It is not known if ENTOCORT EC passes into your breast milk or if it will affect your baby. Talk to your healthcare provider about the best way to feed your baby if you take ENTOCORT EC.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ENTOCORT EC and other medicines may affect each other causing side effects.

How should I take ENTOCORT EC?

- Take ENTOCORT EC exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how many ENTOCORT EC capsules to take. Your healthcare provider may change your dose if needed.
- Take ENTOCORT EC 1 time each day in the morning.
- Take ENTOCORT EC capsules whole. Do not chew or crush ENTOCORT EC capsules before swallowing.
- For patients, unable to swallow a whole capsule, ENTOCORT EC capsules can be opened and administered as follows:
 1. Place 1 tablespoonful of applesauce into a clean container, such as an empty bowl. The applesauce used should not be hot and should be soft enough to be swallowed without chewing.
 2. Open the capsule. You may need to use more than 1 ENTOCORT EC capsule for the dose prescribed by your healthcare provider.
 3. Carefully empty all of the granules inside the capsule on the applesauce.
 4. Stir the granules with the applesauce.
 5. Swallow the applesauce and granules mixture within 30 minutes after preparing it. Follow the applesauce and granules immediately with a glass (8 ounces) of cool water to help with complete swallowing of the granules.

6. Do not chew or crush the granules.
 7. Do not save the applesauce and granules for later use.
- If you take too much ENTOCORT EC call your healthcare provider right away or go to the nearest hospital emergency room.

What should I avoid while taking ENTOCORT EC?

- Do not drink grapefruit juice during your treatment with ENTOCORT EC. Drinking grapefruit juice can increase the level of ENTOCORT EC in your blood.

What are the possible side effects of ENTOCORT EC?

ENTOCORT EC may cause serious side effects, including:

- **Effects of having too much corticosteroid medicine in your blood (hypercorticism).** Long-time use of ENTOCORT EC can cause you to have too much corticosteroid medicine in your blood. Tell your healthcare provider if you have any of the following signs and symptoms of hypercorticism:
 - acne
 - bruise easily
 - rounding of your face (moon face)
 - ankle swelling
 - thicker or more hair on your body and face
 - a fatty pad or hump between your shoulders (buffalo hump)
 - pink or purple stretch marks on the skin of your abdomen, thighs, breasts and arms
- **Adrenal suppression.** When ENTOCORT EC is taken for a long period of time (chronic use), adrenal suppression can happen. This is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal suppression include: tiredness, weakness, nausea and vomiting and low blood pressure. Tell your healthcare provider if you are under stress or have any symptoms of adrenal suppression during treatment with ENTOCORT EC.
- **Worsening of allergies.** If you take certain other corticosteroid medicines to treat allergies, switching to ENTOCORT EC may cause your allergies to come back. These allergies may include a skin condition called eczema or inflammation inside your nose (rhinitis). Tell your healthcare provider if any of your allergies become worse while taking ENTOCORT EC.
- **Increased risk of infection.** ENTOCORT EC weakens your immune system. Taking medicines that weaken your immune system makes you more likely to get infections. Avoid contact with people who have contagious diseases, such as chicken pox or measles, while taking ENTOCORT EC. Tell your healthcare provider right away if you come in contact with anyone who has chicken pox or measles.
- Tell your healthcare provider about any signs or symptoms of infection during treatment with ENTOCORT EC, including:
 - fever
 - pain
 - aches
 - chills
 - feeling tired
 - nausea and vomiting

The most common side effects of ENTOCORT EC in adults include:

- headache
- stomach area (abdominal) pain
- infection in your air passages (respiratory infection)
- gas
- nausea
- vomiting
- back pain
- tiredness
- indigestion
- pain
- dizziness

The most common side effects of ENTOCORT EC in children 8 to 17 years of age, who weigh more than 55 pounds (25 kg), are similar to the most common side effects in adults.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ENTOCORT EC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ENTOCORT EC?

- Store ENTOCORT EC at room temperature between 68°F to 77°F (20°C to 25°C).

- Keep ENTOCORT EC in a tightly closed container.

Keep ENTOCORT EC and all medicines out of the reach of children.

General information about the safe and effective use of ENTOCORT EC.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide or Patient Information leaflet. 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 that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ENTOCORT EC that is written for health professionals.

What are the ingredients in ENTOCORT EC?

Active ingredient: budesonide

Inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres.

The capsule shell contains: gelatin, iron oxide, and titanium dioxide.

Manufactured for and Distributed by:



Allegan, MI 49010

8Z200 RC JX

For more information, go to www.perrigo.com or call 1-866-634-9120.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: January 2019

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021324Orig1s018

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	021324
Submission Date	12/14/2017
Submission Type	Supplement 018 - Labeling
Brand Name	Entocort® EC
Generic Name	Budesonide
Dosage Form and Strength	Capsules, 3 mg
Route of Administration	Oral
Approved Indication	<ul style="list-style-type: none"> • Treatment of mild to moderate active Crohn’s disease involving the ileum and/or the ascending colon, in patients 8 years and older • Maintenance of clinical remission of mild to moderate Crohn’s disease involving the ileum and/or the ascending colon for up to 3 months in adults
Applicant	Perrigo Pharma International DAC
Associated IND	046873
OCP Reviewer	Xinyuan Zhang, Ph.D.
OCP Team Leader	Insook Kim, Ph.D.
Link to EDR	Application 021324 - Sequence 0087 - 0087 (411) 12/14/2017 SUPPL-18 (Labeling) /Multiple Categories/Subcategories

Table of Contents

1. EXECUTIVE SUMMARY	2
1.1 Recommendations	2
2. CLINICAL PHARMACOLOGY ASSESSMENT	2
2.1 Regulatory Background.....	2
2.2 Clinical Pharmacology Findings.....	3
2.3 Outstanding Issues.....	5
2.4 Summary of Labeling Recommendations	5
3. APPENDICES: Individual study review PRG-NT-16-012	5

1. EXECUTIVE SUMMARY

Entocort® EC (budesonide capsules, 3 mg, NDA 021324) was originally approved on 10/02/2001 and indicated for¹:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in adults and pediatric patients 8 years and older
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults

In this supplemental NDA, the applicant proposes to update the Dosage and Administration section of the prescribing information and patient information to include an administration of ENTOCORT EC by sprinkling on applesauce. In addition, the applicant proposes to fulfillment of the Post Marketing Commitment (PMC) 3075-1 as below:

PMC 3075-1: An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.

1.1 Recommendations

The Division of Clinical Pharmacology-3 has found the submission acceptable from a clinical pharmacology standpoint.

The proposed inclusion of the administration method of sprinkling on applesauce in the label is acceptable.

The PMC 3075-1 is fulfilled.

2. CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Regulatory Background

Entocort EC (NDA 021324, budesonide capsules 3 mg) was first approved for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in adults on 10/02/2001². On 4/29/2016, additional indications were approved for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients 8 years of age and older (S012), and for maintenance of remission in Crohn's disease in patients ages birth to 17 years of age (S013)³.

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older

¹ NDA 021324 Entocort EC (budesonide capsules, 3 mg) label approved on 10/14/2017:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021324s016lbl.pdf

² NDA 021324 Entocort EC (budesonide capsules, 3 mg) label approved on 10/02/2001:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21324lbl.pdf

³ Efficacy supplements 012/013 approval letter dated 04/29/2016:
<http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af803e3cd0>

- Adults: 9 mg once daily for up to 8 weeks; repeat 8-week treatment courses recurring episodes of active disease
- Pediatrics 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults
 - Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.

PMC 3075-1 was issued in the approval letter of S012/S013 with a final report submission date of June 30, 2017⁴.

In this submission, the applicant submitted the study report entitled “A single-dose, open-label, two-way crossover study to evaluate the relative bioavailability of Entocort® EC (budesonide) capsules administered as intact capsule versus open capsule granules sprinkled on applesauce, under fasting conditions in normal, healthy, adult, non-smoking male and female subjects ” in fulfillment of the PMC 3075-1, and proposed labeling update based on the study results.

2.2 Clinical Pharmacology Findings

Pharmacology

Budesonide is an anti-inflammatory corticosteroid and has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to glucocorticoid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone¹.

Clinical Pharmacokinetics

Following oral administration of Entocort EC, the time to peak concentration varied in individual patients between 30 and 600 minutes. Mean oral bioavailability of budesonide ranged from 9% to 21% both in patients and in healthy subjects. Budesonide PK was dose-proportional following repeated administration in the dose range of 3 to 15 mg. Concomitant administration of a high-fat meal delayed the time to peak concentration of budesonide from Entocort EC by 2.3 hours but did not significantly affect the AUC in healthy subjects. The mean volume of distribution (V_{ss}) of budesonide varied between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding was 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 was about 0.8. The plasma elimination half-life, after administration of intravenous doses ranged between 2 and 3.6 hours, and did not differ between healthy adults and patients with Crohn's disease.²

Administration of Entocort EC as intact capsule vs. sprinkled on applesauce

The PK after oral administration of 9 mg (3 capsules) Entocort EC administered as open capsule granules sprinkled on applesauce (Treatment A) was compared to that after administration of

⁴ PMR/PMC correspondence dated 04/15/2016:

<http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af803e08ab>

intact capsule (Treatment B). Overall, PK of budesonide after Entocort EC being administered as intact capsule or open capsule granules sprinkled on applesauce were similar and the mean C_{max} and AUC for budesonide met the BE criteria.

The descriptive PK parameters are summarized in Table 1 and the relative bioavailability analysis was summarized in Table 2.

Table 1 Summary of PK parameters after oral administration of 9 mg (3 capsules) Entocort EC administered as intact capsule (Treatment B) versus open capsule granules sprinkled on applesauce (Treatment A). (Source: study report)

Descriptive Statistics of Treatment Means for Budesonide (N = 24)

PK Parameters (Units)	Mean ± SD	
	Entocort-EC 3x3mg capsule contents sprinkled over apple sauce (Treatment A)	Entocort-EC 3x3mg capsules (intact) (Treatment B)
T _{max} (h)*	4.000 (3.000 - 10.000)	3.500 (2.000 - 8.000)
C _{max} (pg/mL)	1453.795 ± 674.8675	1501.224 ± 792.4664
AUC _{0-t} (pg.h/mL)	13239.507 ± 5801.8096	13803.348 ± 7317.8781
AUC _{0-∞} (pg.h/mL)	13583.090 ± 5757.7434	14128.075 ± 7326.4943
λ _z (1/h)	0.126 ± 0.0230	0.116 ± 0.0258
t _½ (h)	5.687 ± 1.1233	6.291 ± 1.5920
AUC_%Extrap_obs (%)	3.093 ± 2.0721	2.877 ± 2.0448
T _{lag} (h)*	0.500 (0.000 - 1.000)	0.500 (0.000 - 2.017)
R ² adjusted	0.992 ± 0.0132	0.991 ± 0.0092

*T_{max} and T_{lag} are represented in median (min-max) value.

Table 2 Summary of relative bioequivalence analysis⁵

PK parameters (n=24)	Reviewer's analysis			Applicant's analysis		
	GMR	90% CI	CV%	GMR	90% CI	CV %
C _{max}	99.89	86.93, 114.79	28.61	99.9	86.93, 114.79	28.6
AUC _t	99.59	90.70, 109.35	19.03	99.2	90.13, 109.22	19.6
AUC _{inf}	99.60	90.70, 109.37	19.04	99.4	90.59, 109.15	19.0
AUC ₀₋₄	94.77	68.93, 130.32	71.48	NA	NA	NA
AUC _{4-t}	99.57	90.03, 110.11	20.52	NA	NA	NA

⁵ The sponsor's 90% CI analysis was submitted on 3/22/2018: <\\cdsesub1\evsprod\nda021324\0090\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\prg-ny-16-012\summary-statistics-0090.pdf>

The sponsor and the reviewer obtained similar results in relative bioavailability analysis comparing C_{max} , AUC_t , and AUC_{inf} . The 90% confidence intervals (CIs) for the Treatment A/Treatment B geometric mean ratios of PK parameters (C_{max} , AUC_t , and AUC_{inf}) met bioequivalence (BE) criteria (Table 2). The reviewer also conducted BE analysis for partial areas under the plasma concentration vs. time profile from 0 to 4 hours (AUC_{0-4}) and from 4 hours to the last measurable time (AUC_{4-t}) as these metrics were also recommended for generic budesonide capsules to ensure profile similarity⁶. The 90% CI for the Treatment A/Treatment B geometric mean ratios of AUC_{4-t} was within the BE limits of 80.00-125.00% (Table 2). The 90% CI for the Treatment A/Treatment B geometric mean ratios of AUC_{0-4} was wider and outside of the BE limits of 80.00-125.00%, presumably due to the high variability (CV% = 71.48) (Table 2). Overall, the results from the submitted relative bioavailability study suggested similar PK of budesonide after Entocort EC being administered as intact capsule or open capsule granules sprinkled on applesauce, and supported the labeling revision.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The sponsor was recommended to add the PK information obtained from the current study in the label as there was no PK information after single dose administration in healthy subjects. The concentration and exposure units were changed from ‘nmol/L’, and ‘nmol*hr/L’ to ‘ng/mL’, and ‘ng*hr/mL’, respectively. The latter units are more commonly used in the labeling. Refer to the final approved labeling.

3. APPENDICES: Individual study review PRG-NT-16-012⁷

Study Information

Study Number	PRG-NT-16-012 ⁸
Protocol Number	PRG-NT-16-012
Study Title	A Single-Dose, Open-Label, Two-Way Crossover Study to Evaluate the Relative Bioavailability of Entocort® EC (budesonide) Capsules Administered as Intact Capsule versus Open Capsule Granules Sprinkled on Applesauce, under Fasting Conditions in Normal, Healthy, Adult, Non-Smoking Male and Female Subjects
Clinical Site (Name & Address)	Clinic, Point-of-Care Testing Facility and Bioanalytical Facility: Lambda Therapeutic Research Inc. (LTRI) 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4.

⁶ Product specific guidance for budesonide capsules:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436975.pdf>

⁷ The individual study review template was modified from the Office of Bioequivalence BE review template.

⁸ [Application 021324 - Sequence 0087 - 5 Clinical Study Reports -](#)

	Tel.: (416) 752-3636; Fax.: (416) 752-7610
Principal Clinical Investigator	Jude Coutinho, M.D. Principal Investigator Lambda Therapeutic Research Inc. 460 Comstock Road, Toronto, Ontario, Canada M1L 4S4. Tel.: (416) 752-3636 Fax.: (416) 752-7610
Dates of the Study	05 July 2017 - 16 July 2017
Analytical Site	(b) (4)
Sample Collection Dates	06 July 2017 - 13 July 2017
Analysis Dates	20 July 2017 - 26 July 2017
Principal Analytical Investigator	(b) (4)
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 06 July 2017 - 26 July 2017 (b) -70 ± 10°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	Long term stability of analyte in human plasma was established for 47 days at -70 ± 10°C & -25 ± 10°C

Product Information (Source: Table 11 of Summary of Biopharmaceutics Studies)⁹

Product	Test	Reference
Treatment ID	A Entocort® EC (budesonide) capsules opened, and granules sprinkled on applesauce (3 x 3 mg)	B Entocort® EC (budesonide) intact capsules (3 x 3 mg)
Product Name	Entocort® EC (budesonide) capsules, 3 mg	Entocort® EC (budesonide) capsules, 3 mg
Manufacturer	AstraZeneca AB	AstraZeneca AB
Batch/Lot No.	HJ0491	HJ0491
Manufacture date	February 2016	February 2016
Expiration Date	31 January 2019	31 January 2019
Strength	3 mg	3 mg
Dosage Form	Capsules	Capsules
Bio-batch size	N/A	N/A
Production Batch Size	266.5 kg	266.5 kg
Potency	3.07 mg/capsule	3.07 mg/capsule
Content Uniformity (mean, %CV)	Meets USP requirements	Meets USP requirements
Dose Administered	9 mg dose (3 x 3 mg)	9 mg dose (3 x 3 mg)
Route of Administration	Oral	Oral

N/A = Not applicable

⁹ [Application 021324 - Sequence 0087 - Summary of Biopharmaceutic Studies - PRG-NY-16-012 \(0087\)](#)

Study Design

Number of Subjects	24
Route / Dose of Administration	Oral / 9 mg (3×3mg)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
Washout Period	7 days
Study Condition	Fasting
Randomization	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Blood Sampling Time Points	pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, 48.0, and 72.0 hours postdose.
IRB Approval	<input checked="" type="checkbox"/> Yes
Length of Fasting	At least 10 hours. No water was permitted from 1.0 hour pre-dose until 1.0 hour post-dose, with the exception of the 240 mL of dosing water. No food was allowed for at least 4 hours post-dose.
Safety Monitoring	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Demographic characteristics

Parameter (Units)	Mean ± SD
	N = 24 (Dosed and included in relative bioavailability evaluation)
Age (years)	43.4 ± 12.79
Height (cm)	169.45 ± 8.310
Weight (kg)	75.07 ± 12.230
BMI (kg / m ²)	26.01 ± 2.714

Dropout information: No dropout.

Study adverse events

Two (2) adverse events (AEs) were reported by one (1) subject during conduct of the study. Both of the AEs were reported in Period-I of the study after administration of Treatment B. Both the AEs were mild in nature. There were no deaths, serious or significant AEs reported during the conduct of the study.

Subjects Experiencing Emesis: None

Bioanalytical Method Validation (Source: Table 4 in Summary of Biopharmaceutics)

Information Requested	Data
Bioanalytical method validation report location	(b) (4)
Analyte	
Internal Standard (IS)	
Method description	
Limit of quantization (pg/mL)	
Average recovery of drug (%) (LQC, MQC & HQC)	
Average recovery of IS (%)	
Standard curve concentrations (pg/mL)	
QC concentrations (pg/mL) (LOQQC, LQC, LMQC, MQC, HQC & DQC)	
QC Intraday precision range (%)	
QC Intraday accuracy range (%)	
QC Interday precision range (%)	
QC Interday accuracy range (%)	
Bench-top stability (hrs)	
Stock stability (days)	
Processed stability (hrs)	
Freeze-thaw stability (cycles)	
Long-term storage stability (days)	
Dilution integrity	
Selectivity	

Sample reanalysis (Source: Table 9 in Summary of Biopharmaceutics)

Study No. Lambda Project No. 0422-17 & Sponsor Protocol No. PRG-NY-16-012, Budesonide Additional information in 5.3.1.4								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	A	B	A	B	A	B	A	B
Pharmacokinetic ⁸	0.0	0.0	0.0 %	0.0 %	0.0	0.0	0.0 %	0.0 %
Significant variations in response of internal standard	1.0	0.0	0.2 %	0.0 %	1.0	0.0	0.2 %	0.0 %
Total	1.0	0.0	0.2 %	0.0 %	1.0	0.0	0.2 %	0.0 %

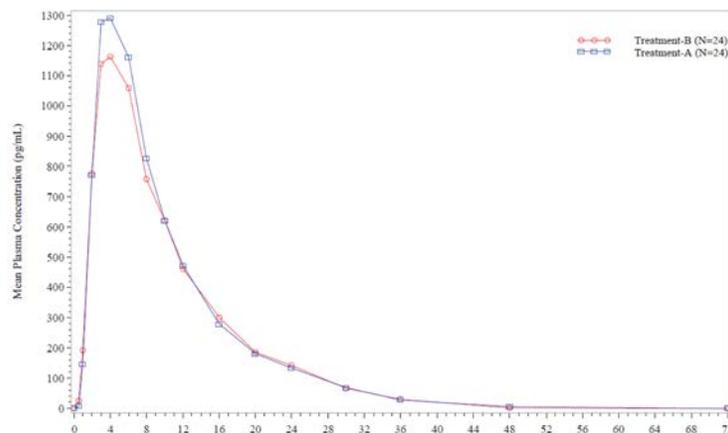
⁸ If no repeats were performed for pharmacokinetic reasons, insert "0.0".
Total assay for Test product (A): 408 and Reference product (B): 407

Incurred sample reproducibility (ISR)

Details of analytical run analyzed for incurred samples	
Date of experiments performed	26 July 2017 to 26 July 2017
Total number of analytical runs analyzed for incurred samples	01
Total number of analytical run reanalyzed for incurred samples along with reason	00
Details of incurred samples reanalyzed	
Total number of samples analyzed during study	815
Total number of samples reanalyzed to establish incurred samples reproducibility	57
Number of incurred samples found within the acceptance criteria	56
Percentage of incurred samples found within the acceptance criteria	98.2 %

Reviewer's comments: LC-MS/MS method was used to analyze plasma budesonide concentrations. The method validation report, sample reanalysis, and IRS results are acceptable. The sample storage duration (20 days) was within the established long term stability duration (47 days).

Mean PK profiles of Treatment A and B



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/s/

XINYUAN ZHANG
05/16/2018

INSOOK KIM
05/16/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021324Orig1s018

OTHER REVIEW(S)

Division of Gastroenterology and Inborn Error Products

REGULATORY PROJECT MANAGER/CLINICAL LABELING REVIEW

Application: NDA 021324/S-018

Submission Dates: December 14, 2017, April 12, 2018, May 30, 2018, August 22, 2018, October 16, 2018, December 14, 2018, and January 15, 2019

Name of Drug: ENTOCORT EC (budesonide)

Applicant: Perrigo Pharma International DAC

Background and Summary Description:

The sponsor submitted a labeling supplement (S-018) on December 14, 2017 to change the Dosage and Administration section of the PI and Patient Information based on the following study submitted to support fulfillment of a Post Marketing Commitment (PMC): *An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.*

Reviews supporting the changes related to the PMC for opening the capsule and sprinkling on soft foods include the following:

- RPM labeling review by Heather Buck dated May 16, 2018
- Clinical Pharmacology review by Xinyuan Zhang dated May 16, 2018
- Division of Medication Error Prevention and Analysis (DMEPA) review by Sherly Abraham dated March 27, 2018
- Division of Medical Policy Programs (DMPP) review by Kelly Jackson dated May 4, 2018

It was also noted during the review of S-018, that that the product is described as a “capsule” in the Product Title:

ENTOCORT[®] EC (budesonide) capsules, for oral use

However, the information in Section 11 Description, describes the product as containing “enteric-coated granules”:

Entocort EC is formulated as hard gelatin capsules filled with enteric-coated granules that dissolve at pH greater than 5.5. 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.

This issue was brought to the attention of the Biopharmaceutics team and the Office of Lifecycle Drug Products (OLDP) in Office of Pharmaceutical Quality (OPQ), and they advised that the product has two release stages (acid stage and buffer stage): it is considered “delayed-release” at the acid stage and “extended-release” at the buffer stage. The Labeling and Nomenclature Committee (LNC) in OPQ advised that when an oral drug product has both delayed and extended modified release characteristics, the product should be labeled as “extended-release” (email dated July 16, 2018 from Rik Lostritto).

On August 22, 2018, as an amendment to this supplement, the sponsor was asked via email to also revise the dosage-form nomenclature in labeling to reflect “extended-release”.

On October 16, 2018, the sponsor submitted a revised PI, PPI and carton/container labeling. In the PI changes were made to the Product Title and the CMC-related sections 3, 11, and 16. The revised Product Title is:

ENTOCORT® EC (budesonide) extended-release capsules, for oral use

The review team (Clinical Pharmacology, DMEPA and DMPP) re-reviewed the labeling and confirmed the change in dosage-form nomenclature to “extended-release capsules”. See also amendment to OPQ/OLDP review for the PI, PPI, and carton/container by Hossein Khorshidi dated December 19, 2018.

The final agreed-upon labeling was submitted by the sponsor on January 15, 2019 and is recommended for approval.

Lawrence Allan

Regulatory Project Manager

Date

Joette M. Meyer, Pharm.D.

Associate Director for Labeling

Date

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/s/

LAWRENCE W ALLAN
01/18/2019 11:06:02 AM

JOETTE M MEYER
01/18/2019 11:08:18 AM
Combined RPM/Clinical Labeling review. I concur.

Division of Gastroenterology and Inborn Errors Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21324/S-018

Name of Drug: ENTOCORT EC (budesonide) capsules

Applicant: Perrigo Pharma International DAC

Labeling Reviewed

Submission and Receipt Date: December 14, 2017

Background and Summary Description:

This Prior Approval Supplement proposes changes to the Dosage and Administration section of the prescribing information and patient information based on the following study submitted in fulfillment of a Post Marketing Commitment: *An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.*

The supplement is due June 14, 2018.

Review

The label that was last approved on October 17, 2017, was compared to the proposed label. The following changes were identified but not annotated:



The changes above were highlighted in the working label and discussed by the team.

Recommendations

From a regulatory standpoint, this supplement is recommended for approval given that the above comments were made to the label and/or discussed by the team.

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/s/

HEATHER G BUCK
05/16/2018

BRIAN K STRONGIN
05/16/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 4, 2018

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ENTOCORT EC (budesonide)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 021324

Supplement Number: S-018

Applicant: Paddock Laboratories, LLC, a Perrigo Company

1 INTRODUCTION

On December 14, 2017, Paddock Laboratories, LLC, a Perrigo Company submitted for the Agency's review a Prior Approval Supplement (PAS) to their New Drug Application (NDA) for ENTOCORT EC (budesonide) capsules, (NDA 021324/S-018). The labeling supplement provides proposed Prescribing Information (PI) changes to the Highlights: Dosage and Administration and Section 2.1 Administration Instructions. Additionally, the Patient Information (PPI) has also been updated with the corresponding revisions to the section "How should I take ENTOCORT EC?"

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology and Inborn Error Products (DGIEP) on January 30, 2018 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for ENTOCORT EC (budesonide) capsules.

2 MATERIAL REVIEWED

- Draft ENTOCORT EC (budesonide) PPI received on December 14, 2017, revised by the Review Division throughout the review cycle and received by DMPP on April 25, 2018.
- Draft ENTOCORT EC (budesonide) Prescribing Information (PI) received on December 14, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on April 25, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KELLY D JACKSON
05/04/2018

MARCIA B WILLIAMS
05/04/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 27, 2018
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 021324/S-018
Product Name and Strength:	Entocort EC (budesonide) capsules, 3 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Perrigo Pharmaceuticals
Submission Date:	December 14, 2017
OSE RCM #:	2018-226
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the prior approval labeling supplement (NDA 021324/S-018) for Entocort EC, submitted on December 14, 2017. The Division of Gastroenterology & Inborn Error Products (DGIEP) requested that DMEPA review the proposed label and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Perrigo Pharmaceuticals submitted a Prior Approval Labeling Supplement (PAS) on December 14, 2017, to update the Dosage and Administration section of the prescribing information (PI) and Patient information based on the fulfillment of postmarketing commitment 3075-1. They are proposing to add an alternate administration option for patients who are unable to swallow an intact capsule (i.e., sprinkling the contents of the capsule on apple sauce for administration). We find the proposed changes to the PI and patient information acceptable from a medication error perspective. We note there are no changes to the currently approved carton labeling and container labels. Additionally, we did not identify any medication error concerns from our search of the previous DMEPA reviews and ISMP Newsletters.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the PI and patient information are acceptable from a medication error perspective and we have no comments at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Entocort EC that Perrigo Pharmaceuticals submitted on December 14, 2017.

Table 2. Relevant Product Information for Entocort EC	
Initial Approval Date	October 2, 2001
Active Ingredient	budesonide
Indication	<p>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 in patients 8 years and older.</p> <p>Maintenance of Clinical Remission of Mild to Moderate Crohn’s Disease (adults): 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 in adults.</p>
Route of Administration	oral
Dosage Form	capsules
Strength	3 mg
Dose and Frequency	<p>Mild to moderate active Crohn’s disease :</p> <ul style="list-style-type: none">•Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses for recurring episodes of active disease.•Pediatrics 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks. <p>Maintenance of clinical remission of mild to moderate Crohn’s disease</p> <ul style="list-style-type: none">•Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.

	<ul style="list-style-type: none"> •When switching from oral prednisolone, begin tapering prednisolone concomitantly with initiating ENTOCORT EC. <p>Hepatic Impairment:</p> <ul style="list-style-type: none"> •Consider reducing the dosage to 3 mg once daily in adult patients with moderate hepatic impairment (Child-Pugh Class B).
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 and are supplied in bottles of 100
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 8, 2018, we searched the L: drive and AIMS using the terms, Entocort EC, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review^a and we confirmed that our previous recommendation was implemented.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 8, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Entocort EC

D.2 Results

We did not identify any articles associated with medication errors or relevant to the labels and labeling for Entocort EC.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Review

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Entocort EC labels and labeling that Perrigo Pharmaceuticals submitted on December 14, 2017.

- Prescribing Information (image not shown)

^aBarlow, M. Label and Labeling Review for Entocort EC (NDA 021324/S-012 & NDA 021324/S-013) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US);.March 7, 2016. 32 p. OSE RCM No.: 2015-1794.

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/s/

SHERLY ABRAHAM
03/27/2018

SARAH K VEE
03/27/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021324Orig1s018

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: Allan, Lawrence
To: "[Jocelyn Clark-Greuel](#)"
Cc: [Briana Hedtke](#)
Subject: NDA 021324/S018 - ENTOCORT EC - Draft labeling comments (11 Jan 2019)
Date: Friday, January 11, 2019 9:27:00 AM
Attachments: [NDA 021324 - ENTOCORT EC - PI \(clean\).docx](#)
[NDA 021324 - ENTOCORT EC - PI \(track changes\).pdf](#)
[NDA 021324 - ENTOCORT EC - PPI \(clean\).docx](#)
[NDA 021324 - ENTOCORT EC - PPI \(track changes\).pdf](#)
[image001.png](#)

Good morning Jocelyn,

At this time we are communicating comments and revisions to the proposed labeling for ENTOCORT. Attached you will find the updated labeling documents; one PDF with revisions and comments marked for your review and one WORD document without. Please use the "clean" WORD files for further edits and resubmission to the application and provide your reply NLT Tuesday, 15 Jan 2019.

Please do not hesitate to contact me if you have any questions concerning the revised labeling.

Regards,

Lawrence Allan
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration
Tel: 240 – 402 – 2786
Fax: 301 – 796 – 9904
lawrence.allan@fda.hhs.gov



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Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters),

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/s/

LAWRENCE W ALLAN
01/11/2019 09:31:43 AM

From: Allan, Lawrence
To: "[Jocelyn Clark-Greuel](#)"
Cc: "[Briana Hedtke](#)"
Subject: NDA 021324/S018 - ENTOCORT EC - Draft labeling comments (12 Dec 2018)
Date: Wednesday, December 12, 2018 3:34:00 PM
Attachments: [image001.png](#)
[NDA 021324 - ENTOCORT EC - PI \(clean\).docx](#)
[NDA 021324 - ENTOCORT EC - PI \(track changes\).pdf](#)
[NDA 021324 - ENTOCORT EC - PPI \(clean\).docx](#)
[NDA 021324 - ENTOCORT EC - PPI \(track changes\).pdf](#)

Good afternoon Jocelyn,

At this time we are communicating comments and revisions to the proposed labeling for ENTOCORT. Attached you will find the updated labeling documents; one PDF with revisions and comments marked for your review and one WORD document without. Please use the "clean" WORD files for further edits and resubmission to the application and provide your reply NLT Friday, 14 Dec 2018.

Please do not hesitate to contact me if you have any questions concerning the revised labeling.

Regards,

Lawrence Allan
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration
Tel: 240 – 402 – 2786
Fax: 301 – 796 – 9904
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you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/s/

LAWRENCE W ALLAN
12/12/2018

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:
CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
Heather Buck RPM, DGIEP

REQUEST DATE:
1/30/2018

NDA/BLA NO.:
NDA 21324/S-018

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
**ENTOCORT® EC
(BUDESONIDE)**

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving
substantially complete labeling)

SPONSOR:
Perrigo Pharma

PDUFA Date: 6/14/2018

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PATIENT PACKAGE INSERT (PPI)
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA/ANDA
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- MANUFACTURING (CMC) SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

<\\CDSESUB1\evsprod\NDA021324\021324.enx>
[Sharepoint](#)

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

This PAS supplement received 12/14/2017 proposes changes to the Dosage and Administration section of the prescribing information and patient information based on the following study submitted in fulfillment of a Post Marketing Commitment: *An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.*

Please review the proposed changes to the PPI once I send you the SCPI. I will schedule a meeting for the review team for some time in April. DMEPA is also consulted.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
01/30/2018

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE, DMEPA

FROM:
Heather Buck RPM, DGIEP

DATE
1/30/2018

IND NO.

NDA NO.
NDA 21324/S-018

TYPE OF DOCUMENT
PAS labeling supplement

DATE OF DOCUMENT
12/14/2017

NAME OF DRUG
ENTOCORT® EC
(BUDESONIDE)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
3/12/18 (negotiable)

NAME OF FIRM: Perrigo Pharma

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | | <input type="checkbox"/> MEDICATION ERRORS |
| <input type="checkbox"/> MEETING PLANNED BY | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

This PAS supplement proposes changes to the Dosage and Administration section of the prescribing information and patient information based on the following study submitted in fulfillment of a Post Marketing Commitment: *An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.*

Please review the proposed changes. I will schedule a meeting for some time in April. DMPP will be consulted for the PPI. A clinical and clin pharm reviewer will also be assigned.

Details

Entocort (budesonide)

NDA 021324/S-018

Stamp Date: 12/14/2017

Due Date: 6/14/18

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[Sharepoint](#)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

HEATHER G BUCK
01/30/2018



NDA 21324/S-018

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

Perrigo Pharma International DAC
Attention: Jocelyn Clark-Greuel
Regulatory Affairs Sr. Manager
3940 Quebec Avenue North
Minneapolis, MN 55427

Dear Ms. Clark-Greuel:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21324
SUPPLEMENT NUMBER: S-018
PRODUCT NAME: Entocort EC (budesonide) capsules
DATE OF SUBMISSION: December 14, 2017
DATE OF RECEIPT: December 14, 2017

This supplemental application proposes changes to the Dosage and Administration section of the prescribing information and patient information based on the following study submitted in fulfillment of a Post Marketing Commitment: *An in-vivo study to compare pharmacokinetics of budesonide after administration of ENTOCORT EC (budesonide) as whole capsules and as granules sprinkled on soft food such as apple sauce or apple juice.*

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2018, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be June 14, 2018.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HEATHER G BUCK
12/21/2017