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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	July 16, 2018
Safety Evaluator:	Amy Chen, PharmD Division of Pharmacovigilance (DPV-I)
Medical Officer:	Ivone Kim, MD, FAAP DPV-I
Team Leader:	Mihaela Jason, PharmD, BCPS DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, MS, BCPS DPV-I
Product Name:	Entocort® EC (budesonide) capsule
Pediatric Labeling Approval Date:	April 29, 2016
Application Type/Number:	NDA 021324
Applicant/Sponsor:	Perrigo Pharma
OSE RCM #:	2018-955

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Entocort® EC (budesonide) in pediatric patients through age <17 years. The Division of Pharmacovigilance (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Entocort® EC (budesonide) capsules in pediatric patients.

Entocort EC was first approved in 2001 and is indicated for 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. The approved pediatric labeling is 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.

DPV-I reviewed all serious FAERS reports with Entocort in the pediatric population through < 17 years of age during the period of October 2, 2001 to April 21, 2018, and identified two cases for our case series. Of the reports reviewed, there were no safety signals identified and there was no increase in the severity or frequency of any labeled adverse events.

The majority of reports described adverse events consistent with the known risks in labeling (e.g., Cushing's syndrome, growth retardation, osteoporosis), described adverse events related to underlying comorbidities (e.g., abnormal hepatic enzymes in a liver transplant patient with a history of fluctuating liver enzymes, malnutrition and weight loss in a patient with history of Crohn's disease), or contained limited information which precluded a meaningful causality assessment.

DPV-I identified one case resulting in death that was possibly related to complications from underlying IBD and in which the extent of Entocort's contribution to the event is unknown due to missing clinical details. The other case in our series reported acute pancreatitis, but the case was confounded by concomitant therapy (mesalazine) that is labeled for pancreatitis.

There is no evidence from these data that there are pediatric safety concerns with Entocort EC (budesonide) at this time. DPV-I recommends no regulatory action at this time and will continue to monitor adverse events associated with Entocort EC (budesonide) use.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Entocort® EC (budesonide) in pediatric patients through <17 years old. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Entocort® in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Entocort® EC (budesonide) is a corticosteroid indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon in patients 8 years and older. Entocort was approved by the FDA for use in adult and pediatric patients on October 2, 2001 and April 29, 2016, respectively. The recommended dosage of Entocort in pediatric patients 8 to 17 years of age who weigh more than 25 kg is 9 mg once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks. It is supplied as an enteric-coated capsule containing 3 mg of budesonide.

Safety and efficacy data used for the approval of the Entocort pediatric indication was partially extrapolated from evidence from induction trials in adults and by the two pediatric studies described below.[1]

1) A randomized, double-blind, active controlled study to evaluate the efficacy of Entocort compared with prednisolone in children 8 to 17 years of age who weigh more than 25 kg with Crohn's disease. Entocort's efficacy was supported by 55% of patients treated with Entocort reaching the endpoint of Crohn's Disease Activity Index (CDAI) ≤ 150[a] compared to 68% of patients treated with prednisolone.[3,4] Adverse reactions reported in pediatric patients were similar to those reactions described in adult patients and no new safety concerns were identified.[1]

2) A pharmacokinetic (PK) study comparing Entocort and its effects on cortisol secretion in pediatric and adult subjects with Crohn's disease following administration of Entocort 9 mg per day for seven days. Entocort systemic exposure and cortisol suppression were slightly greater in pediatric than in adult patients.[1]

This PREA review was triggered by approval of the pediatric indication.

[a] Crohn's Disease Activity Index (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).[2] Active Crohn's disease was defined as CDAI ≥ 200.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

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 (≥ 5%) in adults are: headache, respiratory infection, nausea, back pain, dyspepsia, dizziness, abdominal pain, flatulence, vomiting, fatigue, and pain. (6.1) (6)

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)

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1.

Table 2.1.1 FAERS Search Strategy*

Date of Search	April 21, 2018
Time Period of Search	October 2, 2001† to April 21, 2018
Search Type	Quick Query
Product Name(s)	Product Name: Entocort EC, Entocort
Search Parameters	NDA: 021324

* See Appendix A for a description of the FAERS database.
† U.S. Approval date

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1 presents the number of adult and pediatric FAERS reports from October 2, 2001 to April 21, 2018 with Entocort.

Table 2.2.1 Total Adult and pediatric FAERS reports* from October 2, 2001 to April 21, 2018 with Entocort

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥17 years)	752 (514)	433 (197)	10 (5)
Pediatrics (0 - <17 years)	36 (21)	**26‡ (8)**	3 (0)

* May include duplicates and transplacental exposures, and have not been assessed for causality

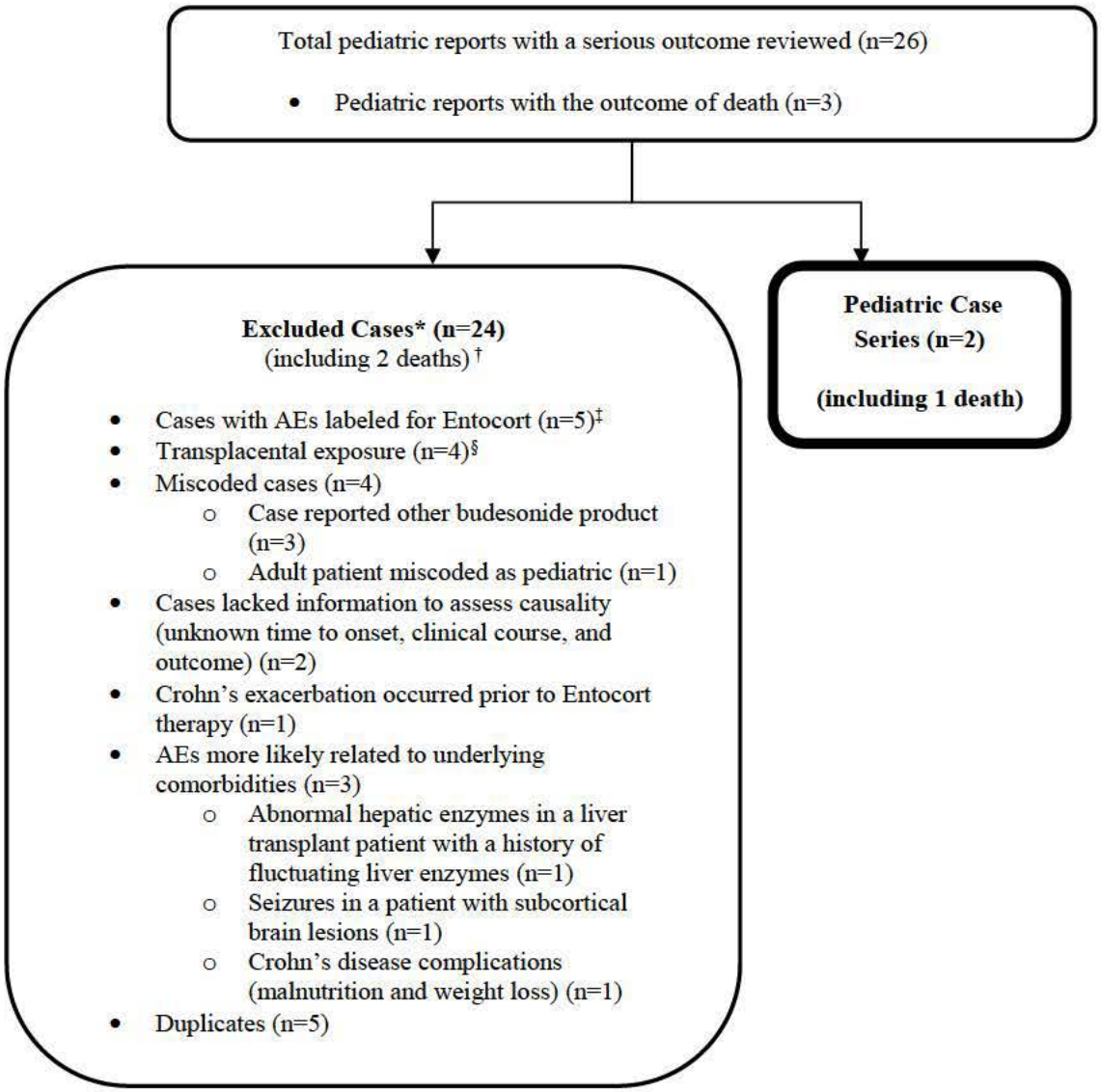
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡ See Figure 2.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 26 pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4.**

Figure 2.2.2 Selection of Serious Pediatric Cases with Entocort



* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above.
† The two cases resulting in death were excluded because they were both duplicate reports of the case described in the case series.
‡ The labeled AEs included (more than one AE per case): Cushing's syndrome (2), intracranial pressure increased (1), drug interaction[5] (1), secondary hypertension (1), adrenal insufficiency (1), growth retardation (1), osteoporosis (1), cushingoid features (1), edema (1).
§ There were three transplacental exposure cases plus one duplicate report. One case described transplacental exposure to concurrent HIV medications (medically induced abortion was performed due to fetal growth retardation). Second case described tooth hypoplasia following transplacental exposure to concurrent prednisolone and azathioprine. Third case described congenital heart defect following transplacental exposure to concurrent azathioprine.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=1)

FAERS Case# 3983585, Mfr# 2003SE03422, Foreign, Expedited, FDA Received Date 7/31/2003

A 16-year-old male with a history of chronic inflammatory disease of the colon received treatment with mesalazine and prednisolone for over 6 months and subsequently developed steroid dependency. He weaned off prednisolone and switched to mesalazine, azathioprine, and Entocort. The patient tolerated a gradual taper of his Entocort without worsening of his baseline of three to four diarrheal stools per day and the drug was discontinued after a total of 3 months of therapy. One to two days prior to the end of Entocort taper, the patient developed vomiting with epigastric pain and was hospitalized; he was afebrile and had no change from baseline IBD symptoms. Mesalazine and azathioprine therapies were suspended and the patient required morphine to alleviate worsening epigastric pain. The patient developed hemodynamic instability, respiratory failure, and died four days after symptom onset and one day after Entocort discontinuation. Autopsy revealed "disseminated intravascular coagulation (DIC) with thrombus in the small vessels of the gastric wall, liver, lungs, myocardium, spleen, and regional lymph nodes were seen" and "a large area of hemorrhage, necrosis, and thickening of the gastric wall was identified." One of two post-mortem blood samples grew "apathogenic streptococcus," but no bacteria was identified on microscopic analysis of the gastric wall. The reporter posits that death may be due to phlegmon in the gastric wall with secondary DIC.

Reviewer's comments: Increased risk of infection is labeled in the "Warnings and Precautions" Section 5.3, "Adverse Reactions," and "Patient Counseling" sections of the Entocort product label. This provides a plausible mechanism for phlegmon development that seeds the bloodstream and leads to sepsis with secondary DIC as suggested by the reporter. However, the narrative lacks additional information to substantiate this hypothesis or to rule out other etiologies for DIC and alternative causes for death such as circulatory collapse due to adrenal insufficiency following prolonged steroid use. Abscess formation is a potential complication of IBD; abscesses are more common in patients with Crohn's disease but can also be seen in patients with ulcerative colitis. A compelling possibility is that the patient was developing IBD-related abscess with sepsis, as the inflammation from his underlying disease was less controlled with the gradual steroid withdrawal. It is not possible to determine the extent to which Entocort contributed to the death given the lack of additional history, laboratory, and diagnostic information.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=1)

2.4.1 Unlabeled Event: Acute pancreatitis (n=1)

FAERS Case # 6045616, Mfr #2006CG00836, Foreign, Expedited, FDA Received 7/31/2003

An 8-year-old female with a history of Crohn's disease received mesalazine for three years after which she was in remission for five years. She started treatment with Entocort 9 mg daily and mesalazine 2 grams daily for a flare-up. Seventeen days after initiating this regimen she was hospitalized for abdominal pain; her diagnostic evaluation included an abdominal ultrasound that was unremarkable and the patient was discharged after symptomatic improvement with acetaminophen treatment. Two days later, the patient was readmitted with vomiting and abdominal pain radiating to the back. Laboratory evaluation revealed blood lipase increased to 4.9 x upper limit of normal (ULN) and amylase to 1.44 x ULN (actual laboratory values unknown), normal transaminases, gamma-glutamyltransferase (GGT), triglycerides, and cholesterol levels. Abdominal ultrasound showed "increased size and heterogeneity of the pancreas" and abdominal CT scan showed "duodenal wall thickening without necrosis." The patient was diagnosed with pancreatitis and her treatment included suspension of Entocort and mesalazine therapy and switch from oral to enteral feeding. The patient's abdominal pain improved within 24 hours

and pancreatic enzymes returned to normal within 72 hours; the patient was discharged from the hospital after initiation of hydrocortisone acetate enema and azathioprine treatment.

Reviewer's comments: This case supports a temporal association between the initiation of Entocort and the onset of acute pancreatitis. However, the case is confounded by concomitant mesalazine use which is labeled for pancreatitis in the "Adverse Reactions" Section 6.1.

3 DISCUSSION

We reviewed all serious FAERS reports with Entocort in the pediatric population through < 17 years of age during the period of October 2, 2001 to April 21, 2018, and identified two cases for our case series. Of the reports reviewed, there were no safety signals identified and there was no increase in the severity or frequency of any labeled adverse events.

The majority of reports described adverse events consistent with the known risks in labeling (e.g., Cushing's syndrome, growth retardation, osteoporosis), described adverse events related to underlying comorbidities (e.g., abnormal hepatic enzymes in a liver transplant patient with a history of fluctuating liver enzymes, malnutrition and weight loss in a patient with history of Crohn's disease), or contained limited information which precluded a meaningful causality assessment.

We identified one case resulting in death that was possibly related to complications from underlying IBD and in which the extent of Entocort's contribution to the event is unknown due to missing clinical details. The other case in our series reported acute pancreatitis, but the case was confounded by concomitant therapy (mesalazine) that is labeled for pancreatitis.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Entocort EC (budesonide) at this time.

5 RECOMMENDATIONS

DPV-I recommends no regulatory action at this time and will continue to monitor adverse events associated with Entocort EC (budesonide) use.

6 REFERENCES

1. L. Perrigo Company. Entocort EC Package Insert. December 2017.
2. Best WR, Becktel 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.
3. Dannis MF. Clinical Review sNDA 021324. Entocort EC (budesonide). April 11, 2016.
4. Radden E. Memorandum and Pediatric Labeling Review. Entocort EC (budesonide). April 5, 2016.
5. Munoz-Cortes A, Montesdeoca C, Boada-Fernandez del Campo. Interaction Between Voriconazole and Budesonide with Clinical Relevance (Cushing's Syndrome). Basic and Clinical Pharmacology and Toxicology 2011;109(3): 41-71.

7 APPENDICES

7.1 APPENDIX A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 Appendix B. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For budesonide case series (N=2)

FAERS CASE NUMBER	FAERS VERSION NUMBER	MANUFACTURER CONTROL NUMBER
3983585	3	2003SE03422
6045616	3	2006CG00836

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/

AMY I CHEN
07/16/2018

IVONE E KIM
07/16/2018

MIHAELA P JASON
07/17/2018

MONICA MUNOZ
07/17/2018