CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021324Orig1s008

Trade Name:	ENTROCORT EC
Generic or Proper Name:	Budesonide
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	June 22, 2009
Indication:	ENTOCORT EC is indicated for: • the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and • the maintenance of clinical remission of mild to moderate Crohn’s disease involving the ileum and/or the ascending colon for up to 3 months.

CENTER FOR DRUG EVALUATION AND RESEARCH

021324Orig1s008

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APPLICATION NUMBER:

021324Orig1s008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-324/S-008

AstraZeneca Pharmaceuticals LP
Attention: George A. Kummeth
Senior Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

Please refer to your supplemental new drug application dated and received October 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entocort EC® (budesonide) Capsules.

We acknowledge receipt of your submissions dated January 13, January 22, and May 5, 2009.

This supplemental new drug application provides for revisions to the prescribing information for Entocort EC based on supporting documentation regarding nursing mothers and anaphylactic reactions.

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

We recommend that you conduct a milk-only lactation study (with or without limited infant sampling) in a subset of women using Entocort EC who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of budesonide in breast milk and any effects on the nursing infant.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling and labeling submitted May 5, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-324."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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 Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Ruyi He, M.D.
Acting Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Ruyi He

6/22/2009 01:07:35 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021324Orig1s008

LABELING

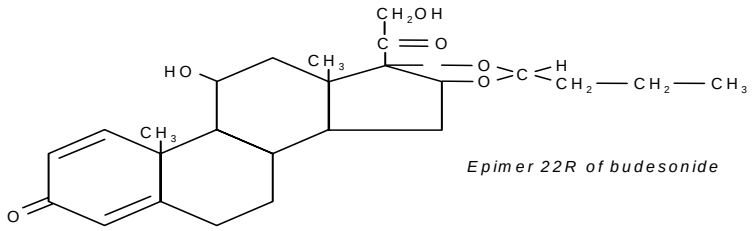
30029-XX

Entocort® EC
(budesonide) Capsules

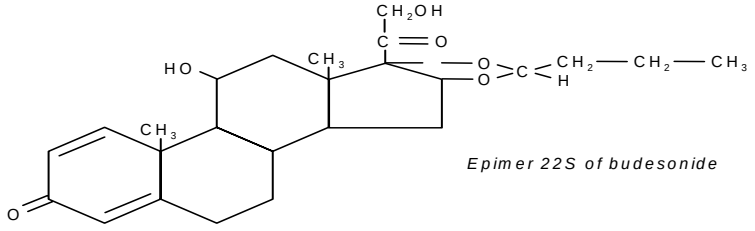
Rx only

DESCRIPTION

Budesonide, the active ingredient of ENTOCORT® EC capsules, is a synthetic corticosteroid. It is designated chemically as (RS)-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Epimer 22R of budesonide



Epimer 22S of budesonide

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

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

CLINICAL PHARMACOLOGY

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

Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

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

In vivo investigations with intravenous doses in healthy subjects are in agreement with the *in vitro* findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. Similarly, high plasma clearance values have been shown in patients with Crohn’s disease. These high plasma clearance

values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

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

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

Special Populations
No significant pharmacokinetic differences have been identified due to sex.

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

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

Drug-Drug Interactions
Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several fold. Co-administration of ketoconazole results in an eight-fold

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

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

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

PHARMACODYNAMICS

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

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

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

CLINICAL STUDIES

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

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

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

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

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

Two placebo-controlled clinical trials (Studies 2 and 3) were conducted. Study 2 involved 258 patients and tested the effects of graded doses of ENTOCORT EC (1.5 mg bid, 4.5 mg bid, or 7.5 mg bid) versus placebo. At baseline, the median CDAI was 290. The 3 mg per day dose level (data not shown) could not be

differentiated from placebo. The 9 mg per day arm was statistically different from placebo (Table 1), while no additional benefit was seen when the daily ENTOCORT EC dose was increased to 15 mg per day (data not shown). In Study 3, the median CDAI at baseline was 263. Neither 9 mg qd nor 4.5 mg bid ENTOCORT EC dose levels was statistically different from placebo (Table 1).

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

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

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

INDICATIONS AND USAGE

ENTOCORT EC is indicated for

- the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

PRECAUTIONS

General

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

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

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

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

Information for Patients

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

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

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

Drug Interactions

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, etc.) is indicated, reduction of the budesonide dose should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. As with other drugs primarily being metabolized through CYP3A4, ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Pregnancy

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

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

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

Nursing Mothers

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

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

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

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

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

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

The safety of ENTOCORT EC was evaluated in 651 patients in five short-term, active disease state studies. They ranged in age from 17 to 74 (mean 35), 40% were male and 97% were white,

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

Table 2: Adverse Events Occurring in ≥ 5% of the Patients in any treated group

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

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

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

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

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

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

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

Glucocorticosteroid Adverse Reactions

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

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

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

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

*Statistically significantly different from ENTOCORT EC 9 mg

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

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

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

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

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

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

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

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

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

CLINICAL LABORATORY TEST FINDINGS

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

The recommended adult dosage for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to

8 weeks. Repeated 8 week courses of ENTOCORT EC can be given for recurring episodes of active disease.

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

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

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

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

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

HOW SUPPLIED

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

They are supplied as follows:

NDC 65483-702-10 Bottles of 100

Storage

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

Keep container tightly closed.

REFERENCES

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

Manufactured by:
AstraZeneca AB
S-151 85 Sodertalje, Sweden

Distributed by:
Prometheus Laboratories Inc.
San Diego, CA 92121

Product of Sweden

EN004B05
30029-XX
Rev XX/XX

PATIENT INFORMATION

ENTOCORT EC (budesonide) Capsules

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

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

Who should not take ENTOCORT EC?

Do not take ENTOCORT EC if:

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

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

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

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

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

How should I take ENTOCORT EC?

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

What should I avoid while taking ENTOCORT EC?

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

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

What are the side effects of ENTOCORT EC?

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

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

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

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

Call your provider if:

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

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

What is Crohn's disease?

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

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

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

General advice about prescription medicines

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

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

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

Manufactured by:
AstraZeneca AB
S-151 85 Södertälje, Sweden

Distributed by:
Prometheus Laboratories Inc.
San Diego, CA 92121

Product of Sweden

EN004B05
30029-XX
Rev XX/XX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021324Orig1s008

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY PRODUCTS

MEDICAL OFFICER'S LABELING REVIEW

Application Type	NDA
Submission Number	21-324
Submission Code	S008
Date:	April 29, 2009
To:	Donna Griebel, MD Director Division of Gastroenterology Products
From:	Aisha Peterson, MD, MPH, MBA Medical Reviewer Division of Gastroenterology Products
Through:	John Hyde, MD, PhD Medical Team Leader Division of Gastroenterology Products
Subject:	Review of proposed labeling changes for Entocort EC

I. Recommendation on Regulatory Action

It is the recommendation of this reviewer that the labeling for Entocort EC be updated to:

a. Include "anaphylactic reactions" in the Postmarketing events sub-section of the ADVERSE REACTIONS section.
b. Provide information in the PRECAUTIONS section regarding infant exposure to budesonide in breast milk based on a clinical trial done using Pulmicort Turbuhaler (dry powder budesonide for inhalation).
c. (b) (4)

See, Entocort EC label, updated May 2009, for finalized label revisions.

II. Background Information

Entocort EC (budesonide) Capsules was FDA approved October 2, 2001 for the treatment of mild to moderate active Crohn's disease in adults involving the ileum and/or ascending colon. On 29 April 2005, a supplemental New Drug Application (S-005) to NDA 21-324 was approved which added the indication of maintenance of clinical remission of mild to moderate Crohn's disease in adults involving the ileum and/or ascending colon for up to 3 months. The recommended adult dosage for the treatment of mild to moderate active Crohn's disease is 9 mg once daily for up to eight weeks with repeated courses as necessary. The recommended adult dosage for maintenance of clinical remission is 6 mg once daily for up to three months. The product is available in 3 mg tablets.

With the current submission, labeling supplement (S008) to NDA 21-324, the Applicant seeks to amend the label to include information on post-marketing reports of anaphylaxis and clinical study information regarding the use of budesonide in women while breast-feeding.

III. Rationale for Proposed Labeling Changes

A. ADVERSE REACTIONS

The Applicant is proposing to include the term "anaphylactic reactions" in the Postmarketing Experience sub-section of the ADVERSE REACTIONS section of the label due to information from clinical study safety databases, external safety databases, regulatory safety databases, and the literature.

In searching for cases of anaphylaxis, the Applicant used the Standardized Medical Dictionary for Regulatory Activities (MedDrA) Query (SMQ) 20000021 terms: Anaphylactic reaction, Anaphylactic shock, Anaphylactic reaction, Anaphylactoid shock, Circulatory collapse, Shock, and Type I hypersensitivity. The Applicant conducted each of these searches during the month of February 2008. In total, these searches found two unique cases of anaphylaxis associated with the use of budesonide.

Table 1. Applicant Search Results

Database	Drug product(s)	End Date	Results
Lund, Sweden (home of AstraZeneca research facilities) Clinical Study Database	Entocort	25 Feb 2008	No results found.
Clintrace*, AZ global clinical drug safety database	Entocort	15 Feb 2008	2 SAE reports: "anaphylactoid reaction" and "circulatory collapse".
AERS and SRS	Entocort Budesonide	25 Feb 2008	No results found.
Literature Search (Embase, Medline, AstraZeneca's internal database Planet)	Entocort Budesonide	18 Feb 2008	1 published case report which was the same event as the "anaphylactoid reaction".

*contains all adverse events reports from spontaneous sources (health care professionals, regulatory authorities, literature, consumers, and others).

Case 1: Anaphylactoid Reaction (Case ID 1999AD00491). A 23-year old female with Crohn's disease reacted with tongue and throat swelling along with transpiration, wheezing, bowel complaints and diarrhea. Events occurred five minutes after the patient took the first capsule of Entocort. Subsequent, intracutaneous tests suggest a non-IgE mediated reaction. The patient's previous history included an episode of buccal mucosa and lip swelling within 30 minutes of exposure to mesalamine.

Case 2: Circulatory Collapse (Case ID 2003SE03422). A patient experienced circulatory collapse one to two days after Entocort was discontinued. The circulatory collapse was part of a larger multi-organ failure.

MO Comment: It is unlikely that Case report ID 2003SE03422 establishes anaphylaxis associated with the use of budesonide. The limited information available suggests an underlying medical condition was likely responsible for this patient's symptoms.

Review of this supplement included consultation with the Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DAEA1). At the request of DGP, Ann Corken Mackey, RPh, MPH, conducted a search of the AERS database to search for events of hypersensitivity or anaphylaxis associated with the use of budesonide reported from initiation of marketing through February 19, 2009.

We requested that the search focus on events of the SMQ 200000021 and adverse events associated with at least 2 of these 3 body systems:

a) Respiratory (upper or lower),
b) Dermatologic/Skin,
c) and/or Cardiovascular.

The OSE consultant's search identified 3 additional cases of allergic/hypersensitivity reactions associated with the use of budesonide.

AERS Case# 6072171. A 54 year old male experienced facial edema, tachycardia, and flushing one day after starting budesonide (9 mg oral). The dose was reduced over the next four days and then discontinued. The patient recovered from this hypersensitivity reaction. The day the symptoms started, the patient was hospitalized and diagnosed with pancreatitis. The indication for the use of budesonide was not reported. Some of the patient's concomitant medications included abacavir, lamivudine, ritonavir, and fasamprenavir, suggesting a diagnosis of it HIV/AIDS.

AERS Case# 6395380. A 22 year old female experienced laryngoedema, dyspnea, facial numbness, and whole body itching 12 hours after starting budesonide to treat an unreported indication. The event resolved. There was no other information reported on this foreign case.

AERS Case# 6646712. A 63 year old male experienced dyspnea, erythema, and rash associated with budesonide use to treat Crohn's disease and ulcerative colitis. The patient had been taking budesonide for at least three years previous to this event. The patient also had a past medical history of allergic reaction to mesalamine and rofecoxib. Adverse events associated with this case include described other adverse events including back pain, bone pain, cataract, salivary unknown gland cancer, increased cortisol blood levels, and an unspecified sleep disorders. The patient's concomitant medications included mesalamine. The report in AERS was submitted by a consumer and verified by the patient's physician.

Medical Reviewer's Comment:
The aforementioned cases of allergic reactions and anaphylaxis associated with budesonide make the inclusion of anaphylactic reaction in the post-marketing experience section of the current label appropriate. While not all of these allergic reaction cases reached the level of anaphylaxis, at least one did and providers should be aware of this case in order to most appropriately manage patients who begin to have allergic symptoms.

B. [redacted] PRECAUTIONS

The Applicant is proposing to revise the "Nursing Mothers" sub-sections in both the [redacted] PRECAUTIONS sections of the label to include information regarding infant exposures to budesonide in breast milk. The Applicant is proposing these labeling changes based on a study done in lactating women using an inhaled form of budesonide.

1. Brief overview of study

Astra Zeneca conducted a clinical pharmacology study (D5254C00763) to assess the concentration of budesonide in breast milk and estimate the exposure of to infants. This open-label, single center study was conducted in asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dose levels of 200 or 400 µg twice daily. Eight mothers participated in the study. Plasma and milk samples were taken during the 8 hours after inhalation of budesonide. In addition, a single blood sample was taken from five of the eight infants for analysis of budesonide concentration.

2. Study Results

In the lactating women, the mean maximal concentration of budesonide in plasma was 0.977 nmol/L in the 200 µg group and 1.714 nmol/L in the 400 µg group. The PK profile of budesonide in breast milk was also studied. The concentration of budesonide in milk was always lower than in plasma. The concentration of budesonide in five of the eight nursing infants was also measured. In all of the infants, budesonide plasma concentrations were below the lower limit of quantification (0.0500 nmol/L). Therefore, the plasma concentrations had to be estimated. Assuming 100% bioavailability, the infant budesonide plasma concentrations were estimated to be 600 times lower than in the mothers. Budesonide, like other corticosteroids, is excreted in human milk.

Previous studies have shown that oral budesonide, e.g. Entocort, has a higher bioavailability than inhaled budesonide (39% and 10-15%, respectively). However, because the total dose of oral budesonide in Entocort is higher than the inhaled budesonide dose in Pulmicort, the maximal plasma concentration of Entocort is expected to be higher. It is estimated that the concentration of budesonide found in breast milk after oral administration is 10 times higher than the maximal concentration found in the 400 µg bid group.

In summary, based on data from this inhaled budesonide study, the total daily intake of budesonide by infants from breast milk feeding is expected to be approximately 0.3% to 1% of the dose inhaled by the mother.

MO Comment:
Amending the current Entocort EC label to include information regarding breast-feeding exposure in the infants of mothers taking budesonide is important. The labeling changes should continue to caution that a risk/benefit decision regarding the use of budesonide in nursing mothers should be made on a case by case basis. (b) (4) *I recommend that the Nursing Mothers sub-section be included* (b) (4) *in the PRECAUTIONS section.*

3. Maternal Health Team (MHT) Labeling Recommendations

As part of the DGP review of this labeling supplement, we consulted the Maternal Health Team. Below are the recommendations of MHT consultant, Richardae Araojo, Pharm.D. See the full review in DFS.

a. Locate all Nursing Mothers information in the PRECAUTIONS section (b) (4) .

MO Comment: I agree that all information regarding Nursing Mothers should be in a single location in the label. I have included this in my recommendations above.

b. Include the following information in the Pregnancy sub-section of the label:

> One retrospective database study reported outcomes in eight women who received treatment with oral budesonide during pregnancy. The oral budesonide dose was 6 mg/day in six patients and 9 mg/day in two patients. The average treatment duration ranged from one to eight months. There were no cases of fetal or maternal adverse effects related to budesonide treatment and no congenital malformations in the babies.

MO Comment: Currently, budesonide is a Category C drug. Given that animal studies have shown adverse effects in pregnancy, the inclusion of human data that is neither adequate nor well-controlled is inappropriate at this time.

The inclusion of human data suggesting that there were no cases of fetal or maternal adverse effects in the study related to budesonide could lead providers to ignore the warnings inherent in the animal studies. Until more rigorous human studies are conducted, it is best to leave this information out of the label.

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

/s/

Aisha E Peterson
4/24/2009 07:31:05 PM
MEDICAL OFFICER

John Hyde
5/7/2009 01:55:35 PM
MEDICAL OFFICER

Donna Griebel
5/11/2009 10:33:16 AM
DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021324Orig1s008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Office of Clinical Pharmacology (OCP) Division of Clinical Pharmacology-3 (DCP-3) Tracking/Action Sheet for Formal/Informal Consults**

From: **Tien-Mien Chen, Ph.D.**			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 03/23/09	IND No.: Serial No.:	NDA No. **21-324/S-008**	DATE OF DOCUMENT **10/29/08**	
NAME OF DRUG **[Entocort EC 3 mg Capsule]**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 01/30/09	

NAME OF THE SPONSOR: **[AstraZeneca]**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW):* [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated) ☐ E-mail comments to: ☐Medical ☐Chemist ☐Pharm-Tox ☐Micro ☐Pharmacometrics ☐Others (Check as appropriate and attach e-mail)	☐ Oral communication with Name: [ ] ☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ Formal Review/Memo (attached) ☒ See comments below ☐ See submission cover letter ☐ OTHER *(SPECIFY BELOW)*: [ ]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS: [X]

Background:

Budesonide is a glucocorticosteroid. NDA 21-324 for Entocort (budesonide) EC capsules was approved on 10/02/01 for

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

The recommended adult dosage is 3 x 3 mg capsules QD in the morning for up to 8 weeks. Repeat 8-week courses of Entocort EC can be given for recurring episodes of active disease.

Synopsis:

On 10/29/08, the sponsor submitted a labeling supplement to NDA 21-324 for Entocort EC capsules to support a new subsection "Nursing Mother" [redacted] (b) (4). A clinical pharmacology study No. D5254C00763 that was conducted in Sweden, 2005 using Pulmicort Turbuhaler was also submitted to support the labeling revisions for Entocort EC capsules.

The above clinical pharmacology study had been previously submitted under labeling supplement S-002 to NDA 21-949 (Pulmicort Flexhaler, budesonide inhalation powder, 180 and 90 mcg) on 12/21/06 and reviewed by the Office of Clinical Pharmacology and found acceptable. The "Nursing Mother" subsection was added to Pulmicort Flexhaler labeling on 06/21/07. Therefore, the above clinical pharmacology study No. D5254C00763 is briefly reviewed and the "Nursing Mother" subsection proposed to Entocort labeling are

reviewed here and referenced to those currently approved under NDA 21-949. Please see clinpharm revisions (p. 6 and 12) onto the sponsor's proposed changes for Entocort EC labeling in Appendix 1 for details.

Recommendation:
The labeling supplement S-008 for Entocort EC capsules that was submitted on 10/29/08 under NDA 21-324 has been reviewed by Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3). From OCP perspective, the proposed labeling needs further revisions and the S-008 labeling supplement is acceptable provided that the following Agency's labeling comments are incorporated into the labeling revisions.

OCP Comments: (Need to be sent to the sponsor)
Please see clinpharm labeling revisions in Appendix 1 for details.

SIGNATURE OF REVIEWER: Tien-Mien Chen, Ph.D. **SIGNATURE OF TEAM LEADER: Sue-Chih Lee, Ph.D.**	Date 02/09/09, 03/23/09 Date 02/09/09, 03/23/09
CC.: HFD # [180**]; TL: [**SCL**]**	**Project Manager: H. Buck Date 03/23/09**

NDA 221-324 for Entocort (Budesonide) EC 30 mg Capsules/S-008 Labeling Supplement

Appendix

Agency's Proposed Labeling Revisions (double undelined for sponsor's proposed changes and red underline for Agency's addition)

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

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

/s/

Tien-Mien Chen
3/26/2009 06:49:05 PM
BIOPHARMACEUTICS

Sue Chih Lee
3/26/2009 07:08:35 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021324Orig1s008

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team (MHT) Review

Date: April 14, 2009 **Date Consulted:** March 16, 2009

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Karen Feibus, MD
Team Leader, Pediatric and Maternal Health Staff

To: Division of Gastroenterology Products (DGP)

Drug: NDA 21-324/S-008; Entocort EC (budesonide) Capsules

Subject: Labeling supplement for Entocort EC proposing revisions to the Nursing Mothers subsection of labeling based on data from an open, single center study (Study # D5254C00763).

Materials Reviewed: Data contained in NDA 21-324/S-008

Consult Question: AstraZeneca submitted a labeling supplement to DGP proposing revisions to the Pharmacokinetics and Nursing Mothers subsections of labeling for Entocort EC. These revisions are proposed based on results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 µg bid (Study # D5254C00763).

DGP requests the Maternal Health Team's review of the Nursing Mothers subsection of the Entocort EC label and to provide any specific concerns regarding the use of oral budesonide in nursing mothers.

EXECUTIVE SUMMARY

On October 29, 2008, AstraZeneca submitted a prior approval labeling supplement (NDA 21-324/S-008) to the Division of Gastroenterology Products (DGP) for Entocort EC (budesonide) capsules. Entocort EC is an oral corticosteroid that contains the active ingredient budesonide. Entocort is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon and for maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or ascending colon for up to three months.

The labeling supplement submitted by the sponsor proposes revisions to the (b) (4) Nursing Mothers subsections of labeling based on results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid (Study # D5254C00763). The MHT previously reviewed Study # D5254C00763 in labeling supplements submitted for Pulmicort Respules, Flexhaler, and Rhinocort Aqua (see Appendix A for MHT reviews dated June 28, 2008 and May 9, 2007).

Study # D5254C00763 confirmed that inhaled budesonide is excreted into human milk and showed a mean milk/plasma ratio of 0.46. The estimated daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Assuming complete oral availability of budesonide, the estimated average plasma concentration in the infants would be 600 times lower than the average plasma concentration in the mothers.

Oral budesonide (Entocort) has a lower bioavailability (10-15%) than inhaled budesonide (39%). However, the recommended doses of oral budesonide are higher (up to 9 mg daily) compared to inhaled budesonide (up to 800 μg daily). The maximal concentration of budesonide in plasma after a 9 mg oral dose is about 5-10 nmol/L compared to about 1-2 nmol/L for 800 μg inhaled budesonide. Because the maximal concentration of budesonide in plasma is about 10 times higher with oral budesonide compared to inhaled budesonide and based on the linear relationship between budesonide concentrations in maternal plasma and breast milk, it is estimated that the concentration of oral budesonide in breast milk is up to 10 times higher than that observed with inhaled budesonide. This is a theoretical estimate based on data for inhaled budesonide and there are no human lactation data for oral budesonide. A milk only lactation study in women taking Entocort who choose to breastfeed would provide the most valuable information on the use of Entocort during lactation. However, inclusion of data from Study # D5254C00763 in the Nursing Mothers subsection of the Entocort label may be useful for clinicians in determining the overall risks and benefits of prescribing budesonide in lactating women.

In addition to reviewing the lactation data submitted by AstraZeneca, the MHT conducted a search of the literature for data on Entocort use during pregnancy. One database study was found on the use of Entocort in Crohn's Disease patients during pregnancy. No adverse maternal or fetal outcomes were reported. In addition, no congenital malformations were found in the babies.

Based on the information described above, the MHT has the following recommendations.

Maternal Health Team Response:

1. The MHT recommends that AstraZeneca conduct a milk-only lactation study (with or without limited infant sampling) in a subset of women using Entocort who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of budesonide in breast milk and any effects on the nursing infant. The Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, http://www.fda.gov/cder/guidance/5918dft.pdf, was published in draft form in 2005. Based on public comment and feedback from the November 2007 advisory committee meeting, the Guidance has been modified and has entered clearance for publication as a final guidance. The Maternal Health Team can answer questions surrounding current thinking on protocol design and would be happy to share this draft document with the review division.

2. The proposed addition of the sponsor's study results to the package insert for Entocort is appropriate. The MHT's recommended revisions to the sponsors proposed labeling are provided on pages 9-11 of this review.

INTRODUCTION

On October 29, 2008, AstraZeneca submitted a prior approval labeling supplement (NDA 21-324/S-008) to the Division of Gastroenterology Products (DGP) for Entocort EC (budesonide) capsules. The supplement proposes revisions to the Pharmacokinetics and Nursing Mothers subsections of labeling based on results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 µg bid (Study # D5254C00763). DGP requested the Maternal Health Team's (MHT) review of the Nursing Mothers subsection of the Entocort EC label and to provide any specific concerns regarding the use of oral budesonide in nursing mothers.

BACKGROUND

Entocort EC is an oral corticosteroid that contains the active ingredient budesonide. Entocort is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon and for maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or ascending colon for up to three months. Budesonide is also available as inhaled (Pulmicort Flexhaler and Respules) and intranasal (Rhinocort Aqua) formulations. The principal therapeutic uses of inhaled and intranasal budesonide are:

- Inhaled formulation - maintenance treatment of asthma and maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema.
- Intranasal formulation - management of seasonal or perennial allergic rhinitis.

In December 2006 and April 2007, AstraZeneca submitted labeling supplements to the Division of Pulmonary and Allergy Products (DPAP) proposing revisions to the Nursing Mothers and Pharmacokinetics subsections of labeling for Pulmicort Respules, Flexhaler, and Rhinocort Aqua. These revisions were proposed based on results from an AstraZeneca sponsored open,

single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid (Study # D5254C00763). The Maternal Health Team reviewed these labeling supplements and provided recommendations to DPAP (see Appendix A for MHT reviews dated June 28, 2008 and May 9, 2007). Based on Study # D5254C00763, the labeling supplement for Entocort EC proposes labeling revisions similar to those provided in the labeling supplements for Pulmicort Respules, Flexhaler, and Rhinocort Aqua. Therefore, this review provides comment and labeling recommendations on the sponsor's proposed Nursing Mothers subsection of the Entocort label based on previous MHT reviews and on the oral use of budesonide during lactation. In addition, the MHT will recommend revisions to the sponsor's proposed Pregnancy subsection of the Entocort label based on published literature.

REVIEW OF DATA

Materials reviewed:

- Study # D5254C00763, budesonide lactation data
- Published data on budesonide and breastfeeding (obtained through PubMed search)
- Sponsor's submitted post-marketing data on breastfeeding and Entocort
- Published data on oral budesonide and pregnancy

Review of Budesonide Lactation Data

A brief summary of Study # D5254C00763 and the most clinically relevant results are provided below. Please see APPENDIX A for a full review of Study # D5254C00763.

Brief Summary of Study # D5254C00763

Study # D5254C00763, was an open-label, single-center study that assessed budesonide concentrations in breast milk and plasma from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid. Eight nursing mothers (aged 26 to 34 years) participated in the study. Plasma and milk samples were collected during the eight hours after inhalation of budesonide. In addition, a single blood sample was taken from five of the eight infants (aged two to six months) for analysis of budesonide concentration.

Clinically Relevant Results of Study # D5254C00763

- Mean maximal concentration of budesonide in maternal plasma was 0.977 nmol/L (200 μg group) and 1.713 nmol/L (400 μg group).

- There was a linear relationship between budesonide concentrations in plasma and breast milk. Budesonide concentrations were always less in breast milk than in plasma [mean milk/plasma ratio (based on AUC) was 0.46].

- In all five infants studied, budesonide plasma concentrations were below the lower limit of quantification (0.0500 nmol/L). Therefore, assuming 100% bioavailability (despite adult oral bioavailability being estimated at 10%), the infant budesonide plasma concentrations were estimated to be $1/600^{th}$ of the concentration in maternal plasma. The estimated daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother.

Relevance of Study # D5254C00763 Results for Oral Budesonide Use during Lactation

There are no human data on the use of oral budesonide during lactation; however, the sponsor estimated budesonide concentrations in breast milk following oral administration based on the following information.

Oral budesonide (Entocort) has a lower bioavailability (10-15%) than inhaled budesonide (39%). However, the recommended doses of oral budesonide are higher (up to 9 mg daily) compared to inhaled budesonide (up to 800 μg daily). The maximal concentration of budesonide in plasma after a 9 mg oral dose is about 5-10 nmol/L compared to about 1-2 nmol/L for 800 μg inhaled budesonide. Therefore, the maximal concentration of budesonide in plasma is expected to be higher with oral budesonide compared to inhaled budesonide.

Study D5254C00763 showed that there is a linear relationship between budesonide concentrations in maternal plasma and breast milk. Among infants in study D5254C00763, the estimated average infant plasma concentration was approximately 600 times lower than in the mothers. However, the actual concentration was likely even lower, since bioavailability in the infants was assumed to be 100%. Because the maximal concentration of budesonide in plasma is about 10 times higher with oral budesonide compared to inhaled budesonide and based on the linear relationship between budesonide concentrations in maternal plasma and breast milk, it is estimated that the concentration of oral budesonide in breast milk is up to 10 times higher than that observed with inhaled budesonide in Study D5254C00763. However, this is an estimate based on data for inhaled budesonide.

Published Data on Budesonide and Breastfeeding

To determine if additional published data are available on budesonide exposure during lactation, a Pubmed search was performed using the following search terms:

- Entocort and lactation
- Entocort and breastfeeding
- budesonide and lactation
- budesonide and breastfeeding

One clinically relevant publication by Falt A, et.al[1] was found during search. This article published the results of Astra-Zeneca's Study # D5254C00763. No new information was presented in the publication.

AstraZeneca's Post-marketing Lactation Data for Entocort

AstraZeneca performed a search of their worldwide safety and clinical study database for adverse event reports in breast fed children exposed to Entocort through breast milk (search performed up to February 21, 2008). The search identified one non-serious adverse event consumer report where a breast feeding infant had symptoms of abdominal distress. No causal assessment was provided by the reporter, and AstraZeneca states that the limited information in this case precludes a causal association with maternal budesonide treatment.

[1] Fält A, Bengtsson T, Kennedy B-M, Gyllenberg A, Lindberg B, Thorsson L, Strandgården K. Exposure of infants to budesonide through breast milk of asthmatic mothers. J Allergy Clin Immunol 2007;120:798-802.

Review of Pregnancy Data for Entocort EC

To determine if published data is available on oral budesonide exposure during pregnancy, a Pubmed search was performed using the following search terms:

- Entocort and pregnancy
- Entocort and fetus
- Oral budesonide and pregnancy
- Oral budesonide and fetus

One clinically relevant publication was found during search and is summarized below:

1. **Beaulieu DB, Ananthakrishnan AN, Issa M, Rosenbaum L, et.al. Budesonide induction and maintenance therapy for Crohn's disease during pregnancy. Inflamm Bowel Dis. 2009; 15(1):25-8.**

   The authors conducted a retrospective review of the Inflammatory Bowel Disease (IBD) center database (at a single academic tertiary referral hospital) to identify patients with Crohn's Disease (CD) who received treatment with oral budesonide for induction and/or maintenance of remission during pregnancy from 2001-2006.

   The authors identified a total of eight women who received treatment with oral budesonide during pregnancy. Table 1 below describes their demographic information, CD characteristics, treatment history, and pregnancy outcomes.

TABLE 1. Disease Characteristics and Pregnancy Outcomes of 8 CD Patients Treated with Budesonide During Pregnancy

Patient No.	Disease Location/ Surgical History	Pregnancy Age	Time of Treatment Initiation	Treatment Duration	Budesonide Dose	Concomitant Medications	Outcomes
1	SB-I,S Ileocolectomy with anastomosis	21	1st trimester	1 month	6 mg daily	Azathioprine B12, FA, MVI	Healthy, full term
2	SB/LB-I	31	1st trimester	1st, 2nd, 3rd trimester (6 months)	6 mg daily-failed taper at 26 weeks	B12, FA, MVI	Healthy, full term
3	SB/LB Ileocecal resection with right hemicolectomy	32	1st trimester	1st, 2nd, 3rd trimester (8 months)	6 mg daily	MTX-discontinued prior to conception MVI	Emergent c-section at 35 weeks due to fetal distress, healthy infant
4	SB/LB-I,S	30	1st trimester	1st, 2nd, 3rd trimester	6 mg daily	Azathioprine Miralax, MVI	Healthy, full term
5	SB-S TIR	26	1st trimester	1st, 2nd, 3rd trimester	9 mg daily	Azathioprine MVI	Healthy, full term
6	SB-S TIR	32	3rd trimester	12 weeks	6 mg daily	Miralax, FA, MVI, MTX discontinued prior to conception	Healthy, full term
7	SB-S,F	25	1st trimester	1st, 2nd, 3rd trimester	6 mg daily	TPN- 1st trimester Lovenox	Healthy, full term
8	SB-I,S	25	1st trimester	1st, 2nd, 3rd trimester	9 mg daily	Sulfasalazine, B12, cholestyramine	Healthy, full term

SB, small bowel; LB, large bowel; I, inflammation; S, strictures; F, fistulizing; TIR, terminal ileum resection; FA, folic acid; MVI, multivitamin; MTX, methotrexate; full term, ≥38 weeks.

The oral budesonide dose was 6 mg/day in six patients and 9 mg/day in two patients. The average treatment duration ranged from one to eight months. Seven patients carried their pregnancy to term (38 weeks), while one patient delivered at 35 weeks. There were no cases of spontaneous abortions. One patient underwent an emergent cesarean section while the other seven patients had normal spontaneous vaginal deliveries. There were no cases of fetal or maternal adverse effects related to budesonide treatment (i.e., no adrenal suppression, ocular side effects, hyperglycemia, gestational diabetes, hypertension, preeclampsia, or infectious complications).

The authors concluded that use of budesonide to induce and maintain remission of CD during pregnancy resulted in good clinical outcomes for both mother and baby in this limited population of women.

LABELING
Sponsors Proposed Labeling

(b) (4)

DISCUSSION AND CONCLUSIONS

The study report submitted by AstraZeneca (Study # D5254C00763) provided information on the distribution of budesonide into breast milk and the concentrations of budesonide in nursing infants. The MHT previously reviewed Study # D5254C00763 in labeling supplements submitted for Pulmicort Respules, Flexhaler, and Rhinocort Aqua (see Appendix A for MHT reviews dated June 28, 2008 and May 9, 2007).

Study # D5254C00763 confirmed that inhaled budesonide is excreted into human milk and showed a mean milk/plasma ratio of 0.46. It also demonstrated a linear relationship between maternal serum and breast milk concentrations of budesonide. The estimated daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Assuming complete oral availability of budesonide, the estimated average plasma concentration in the infants would be 600 times lower than the average plasma concentration in the mothers. Actual infant serum levels may be even lower given that the known adult oral bioavailability of budesonide is only 6-13%.

Oral budesonide (Entocort) has a lower bioavailability (10-15%) than inhaled budesonide (39%). However, the recommended doses of oral budesonide are higher (up to 9 mg daily) compared to

inhaled budesonide (up to 800 µg daily). The maximal concentration of budesonide in plasma after a 9 mg oral dose is about 5-10 nmol/L compared to about 1-2 nmol/L for 800 µg inhaled budesonide. Because the maximal concentration of budesonide in plasma is about 10 times higher with oral budesonide compared to inhaled budesonide and based on the linear relationship between budesonide concentrations in maternal plasma and breast milk, the sponsor estimates that the concentration of oral budesonide in breast milk is up to 10 times higher than that observed with inhaled budesonide. This is a theoretical estimate based on data for inhaled budesonide, and there are no human lactation data for oral budesonide. A milk-only lactation study (with or without limited infant sampling) in breastfeeding women taking Entocort would provide valuable information on budesonide concentrations in breast milk and budesonide exposure in the breastfeeding infant with maternal use of Entocort during lactation. However, inclusion of data from Study # D5254C00763 in the Nursing Mothers subsection of the Entocort label may be useful for clinicians in determining the overall risks and benefits of prescribing oral budesonide for lactating women.

In addition to reviewing the lactation data submitted by AstraZeneca, the MHT conducted a search of the literature for data on Entocort use during pregnancy. One database study was found on the use of Entocort in Crohn's Disease patients during pregnancy. No adverse maternal or fetal outcomes (including congenital malformations) were reported, but the study included only eight pregnant women.

Based on the information described above, the MHT has the following recommendations.

RECOMMENDATIONS

1. The MHT recommends that AstraZeneca conduct a milk-only lactation study (with or without limited infant sampling) in a subset of women using Entocort who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of budesonide in breast milk and any effects on the nursing infant. The Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, http://www.fda.gov/cder/guidance/5918dft.pdf, was published in draft form in 2005. Based on public comment and feedback from the November 2007 advisory committee meeting, the Guidance has been modified and has entered clearance for publication as a final guidance. The Maternal Health Team can answer questions surrounding current thinking on protocol design and would be happy to share this draft document with the review division.

2. The proposed addition of the sponsor's study results to the package insert for Entocort EC is appropriate. However, the Maternal Health Team recommends the following revisions to the sponsor's proposed labeling.

   a. The sponsor proposed the following (b) (4) this section should be included under the PRECAUTIONS, Nursing Mothers subsection of labeling (21CFR201.57).

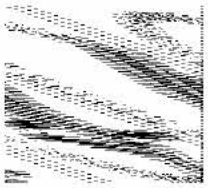
Therefore, we recommend (b) (4)

(b) (4)

b. The following revisions to the sponsors proposed labeling are recommended for the PRECAUTIONS, Pregnancy and Nursing Mothers subsections of labeling:

(b) (4)

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



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: June 28, 2007 **Date Consulted:** April 26, 2007

From: Richardae Araojo, Pharm.D.
Pediatric and Maternal Health Staff

Through: Sandra Kweder, MD
Deputy Director, Office of New Drugs

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Karen Feibus, MD
Team Leader, Pediatric and Maternal Health Staff

To: Division of Pulmonary and Allergy Products (DPAP)/ ODEII

Drug: NDA 20-746/SLR-021: Rhinocort Aqua (budesonide nasal spray)

Subject: Labeling supplement for Rhinocort Aqua proposing revisions to the Nursing Mothers subsection of labeling based on data from an open, single center study (Study # D5254C00763).

Materials Reviewed: NDA 20-746/SLR-021

Consult Question: AstraZeneca submitted labeling supplements to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of labeling for Pulmicort Respules, Flexhaler, and Rhinocort Aqua. In addition, the sponsor has proposed a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of the labels. These revisions are proposed based on results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 µg bid.

DPAP requests the Maternal Health Team's review of the information submitted for Rhinocort Aqua and to provide any specific comments or concerns regarding this application. [Note: The

Maternal Health Team previously reviewed the labeling supplements for Pulmicort Respules and Flexhaler (see Appendix for review dated June 27, 2007)].

EXECUTIVE SUMMARY

Rhinocort Aqua is an intranasal corticosteroid that contains the active ingredient budesonide. The principal therapeutic use of Rhinocort Aqua is for the management of seasonal or perennial allergic rhinitis in adults and children six years of age and older. Rhinocort Aqua is labeled as pregnancy category B and is secreted in human milk.

Budesonide is considered the preferred inhaled corticosteroid for use during pregnancy and has not been associated with an increased risk of congenital malformations. However, data on the use of budesonide during breastfeeding is lacking.

AstraZeneca submitted labeling supplements to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of labeling for Pulmicort Respules, Flexhaler, and Rhinocort Aqua. In addition, the sponsor included a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of the labels. These revisions are proposed based on results from an AstraZeneca sponsored open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid. The labeling supplement for Rhinocort Aqua proposes the same revisions as those provided in the labeling supplements for Pulmicort Respules (NDA 20-929/S-032) and Flexhaler (NDA 21-949/S-002) that were previously reviewed by the MHT (see Appendix for review dated June 27, 2007).

Based on the data from Study # D5254C00763 (N=5), budesonide is minimally excreted into human milk and did not result in any adverse events in the infants exposed. The mean milk/plasma ratio was 0.46 and the estimated daily infant dose of budesonide was 0.3 to 1% of the daily maternal dose.

Maternal Health Team Response:

1. The labeling supplement for Rhinocort Aqua proposes the same revisions as those provided in the labeling supplements for Pulmicort Respules (NDA 20-929/S-032) and Flexhaler (NDA 21-949/S-002) that were previously reviewed by the MHT (see Appendix for review dated June 27, 2007).

2. The proposed addition of the sponsor's study results to the package insert for Rhinocort Aqua is appropriate. The MHT's recommended revisions to the sponsors proposed labeling are provided on pages 5-8 of this review.

3. The Office of Surveillance and Epidemiology (OSE) should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to budesonide via breastmilk.

BACKGROUND

Rhinocort Aqua is an intranasal corticosteroid that contains the active ingredient budesonide. Budesonide exhibits potent glucocorticoid activity and weak mineralocorticoid activity. The principal therapeutic use of Rhinocort Aqua is for the management of seasonal or perennial allergic rhinitis in adults and children six years and older. Rhinocort Aqua is labeled as pregnancy category B and is secreted in human milk.

AstraZeneca submitted labeling supplements to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of labeling for Pulmicort Respules, Flexhaler, and Rhinocort Aqua. In addition, the sponsor included a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of the labels. These revisions are proposed based on results from an AstraZeneca sponsored open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid. The Maternal Health Team reviewed the labeling supplements for Pulmicort Respules (NDA 20-929/S-032) and Flexhaler (NDA 21-949/S-002) on June 27, 2007 (see Appendix for review). This labeling supplement for Rhinocort Aqua proposes the same revisions as those provided in the labeling supplements for Pulmicort Respules and Flexhaler that were previously reviewed by the MHT.

Some experts consider budesonide the preferred inhaled corticosteroid for use during pregnancy based on available safety data including reports from three Swedish Registries.[1] In addition, there are no published reports suggesting increased risk of congenital malformations with the use of inhaled budesonide during early pregnancy. However, data on the use of budesonide during breastfeeding is lacking. The study report submitted by AstraZeneca aims to provide information on budesonide and breastfeeding.

REVIEW OF DATA

Study # D5254C00763 was submitted in the December 18, 2007, labeling supplement for Pulmicort Respules (NDA 20-929/S-032) and the December 21, 2007, labeling supplement for Pulmicort Flexhaler (NDA 21-949/S-002). These supplements were previously reviewed by the Maternal Health Team (see Appendix for review Study # D5254C00763). The April 18, 2007, labeling supplement for Rhinocort Aqua also contains Study # D5254C00763 and proposes the same revisions as those provided in the labeling supplements for Pulmicort Respules and Flexhaler.

DISCUSSION AND CONCLUSIONS

When a breastfeeding mother is on drug therapy for a medical condition the goal is to maximize the infant's benefits from breastfeeding while minimizing the infant's exposure to drug. The American Academy of Pediatrics firmly adheres to the position that breastfeeding ensures the

[1] National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57.

best possible health as well as the best developmental and psychosocial outcomes for infants.[2] The AAP's goals for breastfeeding are consistent with those of Healthy People 2010, the Department of Health and Human Services Blueprint on Action for Breastfeeding, and the United States Breastfeeding Committee's National Agenda.[3] A common reason for the cessation of breastfeeding is the use of medication by the nursing mother and advice by her physician to stop nursing.[3] However, such advice may not be warranted.[3] Breastfeeding should be encouraged whenever possible. Breast milk provides significant health benefits over formula to developing infants and is considered the optimal form of infant nutrition. Breastfeeding associated health benefits include[3]:

- decreased incidence and/or severity of infectious diseases including respiratory tract infections and otitis media
- decreased rates of sudden infant death syndrome
- reduction in the incidence of insulin-dependent and non-insulin dependent diabetes mellitus
- reduction in the incidence of lymphoma, leukemia, Hodgkin disease, hypercholesterolemia, obesity, and asthma
- enhanced cognitive development.

Budesonide has not been associated with an increased risk of congenital malformations, and some maternal-child care experts consider budesonide the preferred inhaled corticosteroid for use during pregnancy. However, published data on the use of budesonide during breastfeeding is lacking. The study report submitted by AstraZeneca (Study # D5254C00763) provided information on the distribution of budesonide into breast milk and the concentrations of budesonide in the nursing infant.

Members of the expert lactation community have generally accepted a relative infant dose value of > 10% of the maternal dose as the threshold for concern. They also acknowledge that a more conservative approach is needed in preterm infants, who have slower drug clearance than full term infants.[4] Inherent toxicity of a drug and doses of the drug used in the pediatric population are other factors that should contribute to the overall risk-benefit assessment of drug use during breastfeeding. Study # D5254C00763 confirmed that orally inhaled budesonide is excreted into human milk and showed a mean milk/plasma ratio of 0.46. The estimated daily infant dose of budesonide was 0.3 to 1% of the daily maternal dose based on the mean and peak budesonide concentrations in breast milk respectively. Assuming complete oral availability of budesonide, the estimated average plasma concentration in the infants would be 600 times lower than the average plasma concentration in the mothers. Actual infant serum levels may be even lower given that the known adult oral bioavailability of budesonide is only 6-13%.

Calculated infant serum budesonide levels can also be compared to serum budesonide levels, in asthmatic children ages four to six years and 10 to 14 years, obtained from studies on inhaled budesonide formulations. The Pulmicort Flexhaler label states that the mean peak steady-state plasma concentrations of budesonide in children 10-14 years of age were 0.4 - 1.5 nmol/L following doses of 180 mcg daily to 360 mcg twice daily. The Pulmicort Respules label states

[2] American Academy of Pediatrics, Policy Statement. Breastfeeding and the Use of Human Milk. Pediatrics. 2005:115(2):496-506.
[3] Hale T. Maternal Medications During Breastfeeding. Clinical Obstetrics and Gynecology. 2004;47(3):696-711.
[4] Ilett K, Kristensen JH. Drug use and breastfeeding. Expert Opin Drug Saf. 2005; 4(4): 745-768.

that the peak plasma budesonide level in 4 to 6 year old asthmatic children was 2.6 nmol/L following a single 1 mg dose. Therefore, serum budesonide levels in breastfeeding infants are ≤ 1% of the levels achieved in asthmatic children (ages 4 to 6 years) treated with budesonide. Based on budesonide concentrations in breast milk and oral bioavailability in Study# D5254C00763, the mean infant serum budesonide concentrations were estimated to be 0.27 - 1.14 pmol/L, which is ≤ 0.4% of the peak serum levels observed in asthmatic children.

We acknowledge that Study # D5254C00763 was conducted in a very small number of lactating asthmatic women (N = 8) and data obtained from only five infants may not fully represent the range of serum levels that might be seen in the general infant population. With this limitation in mind, the results of this study suggest that infant exposure to maternal budesonide through breast milk is minimal. During the study, there were no reported SAEs or discontinuations due to AEs. This finding is consistent with findings from lactation studies conducted with other corticosteroid drug products, such as prednisone and prednisolone.

The recommended daily dose of Pulmicort Flexhaler is 360 to 1440 mcg/day. The recommended daily dose of Rhinocort Aqua is 64 to 256 mcg/day. Approximately 34% of the delivered intranasal dose of Rhinocort Aqua reaches the systemic circulation compared to 39% of the metered dose for orally inhaled Pulmicort Flexhaler. Patients using Rhinocort Aqua use a lower daily dose of budesonide than those using Pulmicort Flexhaler. The lower maternal dose and systemic availability associated with intranasal budesonide use are expected to correlate with a lower relative concentration of budesonide in breast milk among mothers using Rhinocort Aqua compared to mothers using Pulmicort Flexhaler. This, in turn should result in lower total infant daily doses of drug with maternal use of Rhinocort AQ versus either Pulmicort formulation. Based on all available data, the benefits of breastfeeding likely outweigh the potential risks of intra-nasal budesonide exposure for infants.

We also note that the indications for use for Pulmicort and Rhinocort AQ are different and thus, influence the overall risk/benefit decision regarding budesonide use during breastfeeding. Lactating women who use Pulmicort need it to control their asthma. Rhinocort AQ treats the nasal symptoms of allergic rhinitis, which while uncomfortable and inconvenient, are not life threatening. Lactating women have the option to forego treatment with Rhinocort AQ while breastfeeding.

RECOMMENDATIONS

1. This labeling supplement for Rhinocort Aqua proposes the same revisions as those provided in the labeling supplements for Pulmicort Respules (NDA 20-929/S-032) and Flexhaler (NDA 21-949/S-002) that were previously reviewed by the MHT (see Appendix for review dated June 27, 2007).

2. The Office of Surveillance and Epidemiology (OSE) should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to budesonide via breast milk. This report should include available information regarding dose and route of exposure.

3. The proposed addition of the sponsor's study results to the package insert for Rhinocort Aqua is appropriate. The Maternal Health Team recommends the following revisions to the sponsor's proposed labeling for Rhinocort Aqua. Information that has been added to the labeling is underlined. Previous labeling that is recommended for deletion is struckout.

   a. The sponsor proposed the following (b) (4)

(b) (4)

   b. The following revisions to the sponsors proposed labeling are recommended for (b) (4)

(b) (4)

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

References:

1. The National Library of Medicine, Drug and Lactation Database (LactMed) search for budesonide. http://toxnet.nlm.nih.gov/cgi-bin/sis/search.

2. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57.

3. Greenberger PA, Patterson R. The management of asthma during pregnancy and lactation. Clin Rev Allergy. 1987;5:317-24.

4. Ellsworth A. Pharmacotherapy of asthma while breastfeeding. J Hum Lact. 1994;10:39-41.

5. Ilett K, Kristensen JH. Drug use and breastfeeding. Expert Opin Drug Saf. 2005; 4(4): 745-768.

6. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). The use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunol. 2000 May;84(5):475-80.

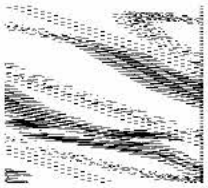
Appendix – MHT review of labeling supplements for Pulmicort Respules (NDA 20-929/S-032) and Flexhaler (NDA 21-949/S-002) dated June 27, 2007.

_____
Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team

_____
Karen Feibus, MD
Team Leader, Maternal Health Team

_____
Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

_____
Sandra Kweder, MD
Deputy Director, Office of New Drugs



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: May 9, 2007 **Date Consulted:** January 16, 2007

From: Richardae Araojo, Pharm.D.
Pediatric and Maternal Health Staff

Through: Sandra Kweder, MD
Deputy Director, Office of New Drugs

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Karen Feibus, MD
Team Leader, Pediatric and Maternal Health Staff

To: Division of Pulmonary and Allergy Products (DPAP)/ ODEII

Drug: NDA 20-929: Pulmicort Respules (budesonide inhalation suspension)
NDA 21-949: Pulmicort Flexhaler (budesonide powder, metered inhaler)

Subject: NDA 20-929/SLR-032; Labeling supplement for Pulmicort Respules proposing revisions to the Nursing Mothers subsection of labeling based on data from an open, single center study (Study # D5254C00763).

Materials Reviewed: NDA 20-929/SLR-032

Consult Question: AstraZeneca submitted a labeling supplement to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of labeling for Pulmicort Respules. In addition, the sponsor has proposed a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of labeling. These revisions are proposed based on the results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid.

DPAP requests the Maternal Health Team's review of the information submitted and asks that they provide any specific comments or concerns regarding this application.

EXECUTIVE SUMMARY

Pulmicort Respules is a corticosteroid suspension for inhalation via jet nebulizer and contains the active ingredient budesonide. The principal therapeutic uses of Pulmicort Respules are maintenance treatment of asthma and prophylactic therapy in children one to eight years of age. Pulmicort is labeled as pregnancy category B.

Budesonide is considered the preferred inhaled corticosteroid for use during pregnancy and has not been associated with an increased risk of congenital malformations. However, data on the use of budesonide during breastfeeding is lacking.

On December 18, 2006, AstraZeneca submitted a labeling supplement to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of the package insert for Pulmicort Respules and a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of labeling. These revisions are proposed based on the results from an open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid (Study # D5254C00763).

Based on the data from Study # D5254C00763 (N=5), budesonide is minimally excreted into human milk and did not result in any adverse events in the infants exposed. The mean milk/plasma ratio was 0.46 and the estimated daily infant dose of budesonide was 0.3 to 1% of the daily maternal dose.

Maternal Health Team Response:

1. The proposed addition of the sponsor's study results to the package insert for Pulmicort Respules is appropriate due to the potential off-label use of this drug in adults. However, data from this study should also be incorporated in the Pulmicort Flexhaler (formerly marketed as Pulmicort Turbuhaler) labeling. The MHT's recommended revisions to the sponsors proposed labeling are provided on pages 10-13 of this review and should be considered for both Pulmicort Respules and Pulmicort Flexhaler.

2. The Office of Surveillance and Epidemiology (OSE) should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to budesonide via breastmilk. This report should include available information regarding dose and route of exposure.

BACKGROUND

Pulmicort Respules is a corticosteroid suspension for inhalation via jet nebulizer and contains the active ingredient budesonide. Budesonide exhibits potent glucocorticoid activity and weak mineralocorticoid activity. The principal therapeutic uses of Pulmicort Respules are maintenance treatment of asthma and prophylactic therapy in children one to eight years of age. Pulmicort is labeled as pregnancy category B. In other countries, Pulmicort Respules are indicated for use in both children and adults.

On December 18, 2006, AstraZeneca submitted a labeling supplement to DPAP proposing revisions to the PRECAUTIONS, Pregnancy, Nursing Mothers subsection of the package insert for Pulmicort Respules. In addition, the sponsor has included a new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of labeling. These revisions are proposed based on the results from an AstraZeneca sponsored open, single center study to assess the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid.

Budesonide is considered the preferred inhaled corticosteroid for use during pregnancy based on available safety data including reports from three Swedish Registries.[1] In addition, there are no published reports suggesting increased risk of congenital malformations with the use of inhaled budesonide during early pregnancy. However, data on the use of budesonide during breastfeeding is lacking. The study report submitted by AstraZeneca aims to provide information on budesonide and breastfeeding.

REVIEW OF DATA

Review of Submitted Materials

Study # D5254C00763 was an open-label, single-center study that assessed the concentration of budesonide in breast milk from asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dosages of 200 or 400 μg bid. This study was sponsored by AstraZeneca and conducted in Sweden by Quintiles Phase I Services. The purpose of the study was to obtain information about the transfer of budesonide from plasma to breast milk in asthmatic women on maintenance treatment with Pulmicort Turbuhaler and to estimate the drug exposure to the nursing infant. The study consisted of two visits to the study center. The following variables were assessed:

- Plasma and milk concentrations of budesonide
- Estimated exposure of budesonide to the infant based on breast milk concentration data
- Milk/plasma concentration ratio of budesonide
- AUC, C_{max}, t_{max} and $t_{1/2}$ for budesonide in plasma and milk
- Milk pH, fat and protein content of breast milk
- If a separate consent was received, plasma concentration of budesonide in a single blood sample from the infant
- Collection of serious adverse events (SAEs) and discontinuations due to adverse events (AEs)

This study was reviewed in detail from a clinical pharmacology perspective by Sayed Al Habet, Ph.D., clinical pharmacology reviewer. The review that follows presents this information from a maternal health perspective.

[1] National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57.

Patients were enrolled into the study if they met the following inclusion criteria:

- Willing and able to comply with study procedures and provide informed consent.
- Breast-feeding women, aged 18 to 45 years inclusive, and having infants aged 1 to 6 months.
- Asthmatics that had been on maintenance treatment with Pulmicort Turbuhaler 200 or 400 μg bid for at least 3 months prior to Visit 2 and have the ability to inhale from Pulmicort Turbuhaler according to given instructions as judged by the investigator or the nurse.

The exclusion criteria for the study were:

- A suspected/manifested infection of HIV, hepatitis B or C or other infection according to WHO Risk classification 2 to 4.
- Significant illness of the infant within the last 2 weeks prior to Visit 1.
- Hospitalization due to exacerbation of asthma within one month prior to Visit 1.
- Respiratory infection within 1 month prior to Visit 1.
- Past (within 1 year) or present alcohol or drug abuse.
- Blood donation during the last three months, heavy loss of blood during childbirth, and having an Hb <115 g/L.
- Pregnancy
- Clinically relevant abnormalities in physical examination, laboratory assessments, blood pressure or pulse as judged by the investigator.
- Clinically relevant disease and/or abnormalities, which in the opinion of the investigator, could either have put the patient or infant at risk because of participation in the study or could have influenced the results of the study or the patients ability to participate in the study.

The women enrolled in the study were trained to ensure correct inhalation technique at visit one and received a diary to record their morning and evening dose of Pulmicort during the two days prior to visit two. Patients were instructed to take their evening Pulmicort dose approximately 12 hours prior to the scheduled dosing at the second clinic visit. Refer to Table 1 in Appendix A for a listing of all data assessments obtained during visit one.

Patients were required to abstain from intake of any prescribed or over the counter medication from one week prior to and during visit two. Long and short acting β_2 agonists, Pulmicort Turbuhaler, and occasional use of acetaminophen (paracetamol) for pain were allowed. Any other medication the investigator felt was necessary for the patient's safety was also permitted.

During the second visit, patients were served a standardized breakfast one hour before study drug administration. Each patient inhaled a single dose of Pulmicort Turbuhaler (200 or 400 μg) according to their usual maintenance dose. Breast milk was collected from one breast pre-dose and at 20 minutes, one hour, three hours, six hours, and eight hours after drug administration. Blood samples were collected for plasma budesonide levels pre-dose and at nine time points after drug administration as shown in the sponsor's Table 2 below. At pre-dose sample collection, breast milk collection began 30 minutes before drug administration and the blood sample was drawn immediately before drug administration. At all other times when blood sampling and breast milk sampling times coincided, blood samples were collected first. Infants were allowed to breastfeed at any time on the breast that was not used for sampling; however the infants who

received consent for sampling were to breastfeed 0.3 to one hour after drug administration if possible.

Table 2 Time schedule for repeated assessments during Visit 2

	Pre-dose	+10 min	+20 min	+40 min	+1 h	+2 h	+3h	+4h	+6 h	+8 h
PK sampling blood	x[a]	x	x	x	x	x	x	x	x	x
Breast milk sampling	x[b]		x		x		x		x	x

a Blood sample was to be taken immediately prior to drug administration.

b Breast milk sampling was to start approximately 30 minutes prior to drug administration.

Only information regarding serious adverse events (SAEs) and discontinuations due to adverse events (AEs) were collected in this study. According to the sponsor, significant AEs of particular clinical importance, other than SAEs and those AEs leading to subject discontinuation were to be classified as *other significant AEs*.

Reviewer comment:

> *The sponsor only reported SAEs and discontinuations due to AEs. Therefore, if an adverse event occurred that did not result in discontinuation of the study it was not recorded or reported.*

The investigators enrolled eight asthmatic breastfeeding women on maintenance treatment with Pulmicort Turbuhaler (200 or 400 µg bid) and their infants. All women were Caucasian. Four women were included at each dose level. The women were 26 to 34 years of age (mean 30.8) and had infants ages two to six months (mean 4.1). All patients completed the study and no SAEs or discontinuations due to AEs were reported. Of the eight infants enrolled, five infants were given consent by their mother to have one single blood sample taken one to 1.5 hours after the first breastfeed following drug administration.

As shown in Appendix A, Table 6, the plasma budesonide AUC and C_{max} of the women enrolled in the study seemed to be proportional to the dose given. The investigators also compared these PK parameter outcomes from lactating women (N = 8) to a reference group of non-lactating women (N = 37) from two previous studies using Pulmicort Turbuhaler 200 µg once daily or 400 µg twice daily. A wider range of variability in C_{max} was seen in this larger non-lactating population; however the median C_{max} value for both lactating and non-lactating women was the same (see Appendix A, Tables 8 and 9). Concentrations of budesonide in breast milk over time were used to calculate AUCs, average and maximum concentrations, and half life (see Appendix A, Tables 10 and 11). These values were used to determine the milk/plasma ratio, the estimated infant daily dose and the infant dose as a percentage of maternal dose. These measures are displayed in Table 12 below. The mean milk/plasma ratio (based on AUC) was estimated to be 0.46. The median milk/plasma ratio was 0.43 (200 µg group) and 0.50 (400 µg group).

Table 12 Summary of estimated infant dose based on breast milk C_{av}

Variable	Pulmicort dose	n	Geometric mean	CV	Min	Median	Max
M/P ratio	200 µg bid	4	0.428	24.5	0.32	0.43	0.58
	400 µg bid	4	0.502	18.6	0.40	0.50	0.62
Daily infant dose (µg/kg/day)	200 µg bid	4	0.0068	25.3	0.005	0.007	0.009
	400 µg bid	4	0.0142	50.7	0.007	0.016	0.021
Daily maternal dose (µg/kg/day)	200 µg bid	4	2.46	17.8	2.1	2.4	3.1
	400 µg bid	4	4.91	14.4	4.1	5.1	5.6
Percentage maternal dose (%)	200 µg bid	4	0.277	30.5	0.21	0.28	0.38
	400 µg bid	4	0.288	55.9	0.15	0.30	0.52
$C_{av,infant}$ (pmol/L)	200 µg bid	4	0.371	25.3	0.27	0.39	0.47
	400 µg bid	4	0.773	50.7	0.39	0.90	1.14
$C_{av,infant}$/ $C_{av,mother}$ (%)	200 µg bid	4	0.151	24.5	0.11	0.15	0.20
	400 µg bid	4	0.177	18.6	0.14	0.18	0.22

Plasma budesonide concentrations were obtained in 5 infants. These samples were taken on average 140 (range 130-154) minutes after budesonide administration to the mother and 87 (range 40-124) minutes after the start of breastfeeding (post-dose). One mother nursed her infant twice after dosing and all others only once. For all infant samples collected, the budesonide concentration was below the limit of quantification (<0.02 nmol/L in 4 infants and <0.04 nmol/L in one infant), depending on the sample volume.

Since actual serum budesonide levels in the infants were lower than the quantifiable assay limit, the sponsor also estimated the infants' exposure to budesonide as shown in Table 12 above. These calculations used the average budesonide concentration in breast milk over the dosing interval, $C_{av,bm.}$ On a kilogram basis, the estimated daily oral dose ingested by the infant (orally received) constituted 0.28% to 0.29% of the maternal (inhaled) dose, depending on dose level. Based on assumed complete oral bioavailability, the estimated mean concentration of budesonide in the infant ranged from 0.27 to 0.47 pmol/L (200 µg dose group) and 0.39 to 1.14 pmol/L (400 µg dose group); about 600 times lower than the average plasma concentration in the mother.

Reviewer comment:

True infant serum budesonide levels may be even lower than those estimated by the sponsor since the known adult bioavailability of budesonide is only 6-13%.

Sponsors conclusions:

- Maintenance treatment with Pulmicort Turbuhaler 200 or 400 µg bid in asthmatic women results in negligible systemic exposure to budesonide in breastfed infants.

- The PK profile of budesonide in lactating women appears to be similar to the PK profile in non-lactating women (based on comparison with historical data).

- The PK profile in breast milk followed the plasma profile, supporting passive diffusion as the mechanism of transfer. The mean milk/plasma ratio (based on AUC) was estimated to be 0.46.

- The estimated daily infant doses of budesonide based on average breast milk concentrations were approximately 0.3% of the daily maternal dose for both dose groups. Based on maximum breast milk concentration, estimated daily infant dose of budesonide was about 1% of the daily maternal dose. Assuming complete oral availability of budesonide, the estimated average plasma concentration in the infants was about 600 times lower than the average plasma concentration in the mothers.

- The budesonide breast milk/plasma concentration ratio increased with increasing fat content but was independent of pH and protein content.

- All measured infant plasma concentrations of budesonide were below the quantifiable limit of the assay.

Reviewer comment:

The sponsor's conclusions seem appropriate based on the data presented in this study. However, the limited sample size and patient demographics of this study may not account for the wider range of variability that may occur in the general population.

Based on the data presented above, AstraZeneca proposes the following revisions to the package insert for Pulmicort Respules:

1. The following new subsection for Nursing Mothers is being proposed under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of labeling:

(b) (4)

Additional Materials Reviewed

A PubMed searched was performed using the following search terms:

- budesonide and breastfeeding
- budesonide and lactation
- asthma and breastfeeding
- asthma and lactation

There was limited relevant published information on the use of budesonide during breastfeeding. The National Library of Medicine's Drug and Lactation Database states that *the amounts of inhaled corticosteroids absorbed into the maternal bloodstream and excreted into breastmilk are probably too small to affect a breastfed infant.*[2] This information is based on review articles and the National Asthma Education and Prevention Program, Asthma and Pregnancy expert panel report, stating that inhaled corticosteroids are not contraindicated in breastfeeding.[1] In addition; much of the information currently available regarding budesonide and breastfeeding is extrapolated from data on prednisone and prednisolone during breastfeeding. According to the American Academy of Pediatrics, prednisone and prednisolone are compatible with breastfeeding.

DISCUSSION AND CONCLUSIONS

When a breastfeeding mother is on drug therapy for a medical condition, the goal is to maximize the infant's benefits from breastfeeding while minimizing the infant's exposure to drug. The American Academy of Pediatrics firmly adheres to the position that breastfeeding ensures the best possible health as well as the best developmental and psychosocial outcomes for infants.[3] The AAP's goals for breastfeeding are consistent with those of Healthy People 2010, the

[2] The National Library of Medicine, Drug and Lactation Database (LactMed) search for budesonide. http://toxnet nlm.nih.gov/cgi-bin/sis/search.

[3] American Academy of Pediatrics, Policy Statement. Breastfeeding and the Use of Human Milk. Pediatrics. 2005:115(2):496-506.

Department of Health and Human Services Blueprint on Action for Breastfeeding, and the United States Breastfeeding Committee's National Agenda.[3] A common reason for the cessation of breastfeeding is the use of medication by the nursing mother and advice by her physician to stop nursing.[4] However, such advice may not be warranted.[4] Breastfeeding should be encouraged whenever possible. Breast milk provides significant health benefits over formula to developing infants and is considered the optimal form of infant nutrition. Breastfeeding associated health benefits include[3]:

- decreased incidence and/or severity of infectious diseases including respiratory tract infections and otitis media
- decreased rates of sudden infant death syndrome
- reduction in the incidence of insulin-dependent and non-insulin dependent diabetes mellitus
- reduction in the incidence of lymphoma, leukemia, Hodgkin disease, hypercholesterolemia, obesity, and asthma
- enhanced cognitive development

Budesonide has not been associated with an increased risk of congenital malformations, and some maternal-child care experts consider budesonide the preferred inhaled corticosteroid for use during pregnancy. However, published data on the use of budesonide during breastfeeding is lacking. The study report submitted by AstraZeneca (Study # D5254C00763) provided information on the distribution of budesonide into breast milk and the concentrations of budesonide in the nursing infant.

Members of the expert lactation community have generally accepted a relative infant dose value of > 10% of the maternal dose as the threshold for concern. They also acknowledge that a more conservative approach is needed in preterm infants, who have slower drug clearance than full term infants.[5] Inherent toxicity of a drug and doses of the drug used in the pediatric population are other factors that should contribute to the overall risk-benefit assessment of drug use during breastfeeding. Study # D5254C00763 confirmed that orally inhaled budesonide is excreted into human milk. The mean milk/plasma ratio was estimated to be 0.46. The estimated daily infant dose of budesonide was 0.3 to 1% of the daily maternal dose based on the mean and peak budesonide concentrations in breast milk respectively. Assuming complete oral availability of budesonide, the estimated average plasma concentration in the infants was 600 times lower than the average plasma concentration in the mothers. This estimate, in all probability, is even lower since 100% bioavailability was assumed in the infant while the known adult oral bioavailability of budesonide is only 6-13%.

For comparison, the Pulmicort Flexhaler label states that the mean peak steady-state plasma concentrations of budesonide in children 10-14 years of age were 0.4 - 1.5 nmol/L following doses of 180 mcg daily to 360 mcg twice daily. The Pulmicort Respules label states that the peak plasma budesonide level in 4 to 6 year old asthmatic children was 2.6 nmol/L following a single 1 mg dose. Therefore, serum budesonide levels in breastfeeding infants are ≤ 1% of the levels achieved in asthmatic children (ages 4 to 6 years) treated with budesonide. Based on budesonide concentrations in breast milk and oral bioavailability in Study# D5254C00763, the mean infant

[4] Hale T. Maternal Medications During Breastfeeding. Clinical Obstetrics and Gynecology. 2004;47(3):696-711.
[5] Ilett K, Kristensen JH. Drug use and breastfeeding. Expert Opin Drug Saf. 2005; 4(4): 745-768.

serum budesonide concentrations were estimated to be 0.27 - 1.14 pmol/L, which is ≤ 0.4% of the peak serum levels observed in asthmatic children.

We acknowledge that Study # D5254C00763 was conducted in a very small number of lactating asthmatic women (N = 8) and data obtained from only five infants may not fully represent the range of serum levels that might be seen in the general infant population. With this limitation in mind, the results of this study suggest that infant exposure to maternal budesonide through breast milk is minimal. During the study, there were no reported SAEs or discontinuations due to AEs. This finding is consistent with findings from lactation studies conducted with other corticosteroid drug products, such as prednisone and prednisolone. Therefore, the benefits of breastfeeding likely outweigh the potential risks of budesonide exposure for infants.

RECOMMENDATIONS

1. Although Pulmicort Respules are indicated only for use in children one to eight years of age, the sponsors proposed addition of the results from Study # D5254C00763 to the package insert for Pulmicort Respules is appropriate due to the potential off-label use of this drug in adults.

2. Data from this study should also be incorporated into the Pulmicort Flexhaler labeling (formerly marketed as Pulmicort Turbuhaler).

3. The Office of Surveillance and Epidemiology (OSE) should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to budesonide via breastmilk. This report should include available information regarding dose and route of exposure.

4. The Maternal Health Team recommends the following revisions to the sponsor's proposed labeling for Pulmicort Respules. The same changes should be made in Pulmicort Flexhaler labeling. Information that has been added to the labeling is underlined. Previous labeling that is recommended for deletion is struck out.

    a. The sponsor proposed the following new subsection for Nursing Mothers under the CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations section of labeling for Pulmicort Respules. (b) (4)

(b) (4)

(b) (4)

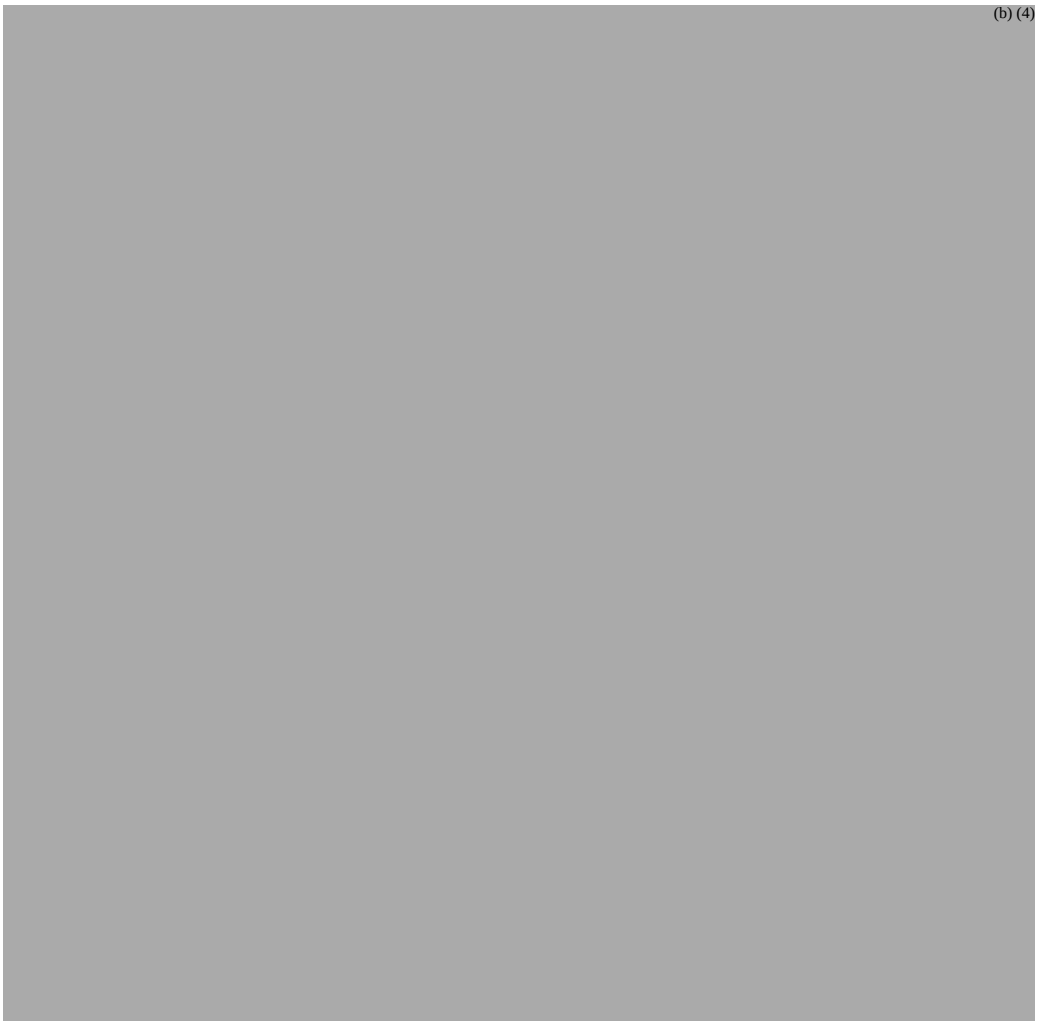
b. The following revisions to the sponsors proposed labeling are recommended for the PRECAUTIONS, Pregnancy, Nursing Mothers subsections of labeling for Pulmicort Respules and Flexhaler:

(b) (4)

(b) (4)

ii. **Pulmicort Flexhaler** - Nursing Mothers:

(b) (4)



References:

1. The National Library of Medicine, Drug and Lactation Database (LactMed) search for budesonide. http://toxnet.nlm.nih.gov/cgi-bin/sis/search.

2. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57.

3. Greenberger PA, Patterson R. The management of asthma during pregnancy and lactation. Clin Rev Allergy. 1987;5:317-24.

4. Ellsworth A. Pharmacotherapy of asthma while breastfeeding. J Hum Lact. 1994;10:39-41.

5. Ilett K, Kristensen JH. Drug use and breastfeeding. Expert Opin Drug Saf. 2005; 4(4): 745-768.

6. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI). The use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunol. 2000 May;84(5):475-80.

APPENDIX A

Table one, six, eight, nine, ten, and eleven from sponsors study report:

Table 1 Study plan

	Visit 1(-21 to -1)	Visit 2 (1)
Informed consent/allocation of enrolment code (patient and infant)	x	
Demographic data (patient and infant)	x	
Medical/surgical history	x	
Inclusion/Exclusion criteria	x	
Physical examination	x	
Vital signs	x	
Clinical chemistry/haematology and urinalysis	x	
Drugs of abuse screen	x	
Pregnancy test	x	
Hepatitis/HIV serology	x	
Practice of inhalation technique	x	
Distribution of diaries	x[a]	
Allocation of patient No./infant No.		x
Drug administration		x
PK sampling (blood)		x[b]
Breast milk sampling		x[b]
Adverse events		x[c]
Body weight of infant		x
Blood sample from infant		x[d]

a Diaries were used to record time of drug inhalation during two days prior to Visit 2.
b Samples were collected pre-dose and repeatedly after drug administration according to Table 2
c Collection limited to SAEs and discontinuations due to AEs.
d Only taken if separate consent was given by parents.

Table 6 **Summary of pharmacokinetic parameters based on plasma budesonide in mothers**

Variable	Pulmicort dose	n	Geo-metric mean	CV	Min	Median	Max
AUC (nmol*h/L)	200 µg bid	4	2.95	14.8	2.7	2.8	3.7
	400 µg bid	4	5.24	31.7	3.3	5.9	6.5
AUC_{0-t} (nmol*h/L)	200 µg bid	4	2.72	15.9	2.5	2.5	3.4
	400 µg bid	4	4.81	32.1	3.1	5.4	6.1
C_{av} (nmol/L)	200 µg bid	4	0.246	14.8	0.22	0.23	0.31
	400 µg bid	4	0.437	31.7	0.28	0.49	0.54
C_{max} (nmol/L)	200 µg bid	4	0.977	21.4	0.73	1.04	1.17
	400 µg bid	4	1.713	44.0	0.92	2.04	2.26
$t_{1/2}$ (h)	200 µg bid	4	2.64	14.9	2.3	2.6	3.1
	400 µg bid	4	2.90	19.0	2.4	2.8	3.8

Table 8 **Comparison of PK parameters based on plasma budesonide between lactating and non-lactating women**

Variable	Patient group[a]	n	Geometric mean	CV	Min	Me-dian	Max
AUC/dose (10^{-3}*h/L)	Lactating	8	5.99	23.6	3.6	6.0	7.9
	Non- lactating	37	5.41	66.2	1.1	5.7	16.4
C_{max}/dose (10^{-3}/L)	Lactating	8	1.97	32.4	1.0	2.2	2.5
	Non- lactating	37	1.78	92.7	0.1	2.2	5.2
$t_{1/2}$ (h)	Lactating	8	2.77	16.6	2.3	2.8	3.8
	Non- lactating	34	3.73	46.6	1.4	3.5	13.3

a Lactating women from present study, non-lactating women from Studies SD-004-0620 and SD-004-0764.

Table 9 **Comparison of age and plasma budesonide t_{max} between lactating and non-lactating women**

Variable	Patient group[a]	n	Arith-metic mean	SD	Min	Median	Max
Age (yrs)	Lactating	8	30.8	2.8	26	31	34
	Non-lactating	37	35.0	8.0	19	35	45
t_{max} (min)	Lactating	8	25.0	13.1	10	20	40
	Non-lactating	37	21.1	22.4	0	10	120

a Lactating women from present study, non-lactating women from Studies SD-004-0620 and SD-004-0764.

Table 10 Summary of pharmacokinetic parameters based on breast milk budesonide

Variable	Pulmicort dose	n	Geo-metric mean	CV	Min	Median	Max
AUC (nmol*h/L)	200 µg bid	4	1.26	25.3	0.9	1.3	1.6
	400 µg bid	4	2.63	50.7	1.3	3.1	3.9
AUC_{0-t} (nmol*h/L)	200 µg bid	4	1.07	31.6	0.8	1.1	1.4
	400 µg bid	4	2.43	52.9	1.2	2.9	3.6
C_{av} (nmol/L)	200 µg bid	4	0.105	25.3	0.08	0.11	0.13
	400 µg bid	4	0.219	50.7	0.11	0.25	0.32
C_{max} (nmol/L)	200 µg bid	4	0.390	23.9	0.28	0.41	0.48
	400 µg bid	4	0.778	51.8	0.40	0.89	1.19
$t_{1/2}$ (h)	200 µg bid	4	2.06	28.3	1.6	2.0	3.0
	400 µg bid	4	2.04	11.4	1.8	2.0	2.3

Table 11 Time to maximum concentration of budesonide in breast milk

Variable	Pulmicort dose	n	Arith-metic mean	SD	Min	Median	Max
t_{max} (min)	200 µg bid	4	31.5	19.7	21	22	61
	400 µg bid	4	43.3	23.4	23	43	65

_____
Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team

_____
Karen Feibus, MD
Team Leader, Maternal Health Team

_____
Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

_____
Sandra Kweder, MD
Deputy Director, Office of New Drugs

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/s/

Chardae Araojo
5/9/2007 12:13:35 PM
CSO

Karen Feibus
5/9/2007 12:15:01 PM
MEDICAL OFFICER

Lisa Mathis
5/24/2007 01:19:58 PM
MEDICAL OFFICER

Sandra L. Kweder
6/27/2007 01:04:42 PM
MEDICAL OFFICER

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/s/

Chardae Araojo
4/21/2009 09:21:02 AM
CSO

Karen Feibus
4/28/2009 11:23:42 PM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review.

Lisa Mathis
5/12/2009 09:07:26 AM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Gastroenterology Products

Application Number: 21-324 / S-008

Name of Drug: ENTOCORT EC© (budesonide) Capsules

Applicant: AstraZeneca Pharmaceuticals LP

Material Reviewed:

Submission Dates: October 29, 2008, January 13, 2009, January 22, 2009

Receipt Dates: October 29, 2008, January 13, 2009, January 22, 2009

Submission Date of Structure Product Labeling (SPL): October 29, 2008[1]

Type of Labeling Reviewed: WORD & SPL

Background and Summary

Entocort EC was first approved October 2, 2001, (labeling in Physician's Labeling Rule (PLR) format is therefore not required until June 30, 2013). The Entocort label was last approved April 29, 2005. The sponsor submitted the present supplement to provide for various changes including revisions to the [redacted] (b) (4) PRECAUTIONS, and ADVERSE EXPERIENCE sections. Errors were found with the original submission and subsequent January 13, 2009, amendment. Correct labels were submitted with the January 22, 2009, amendment. The SPL label (albeit in incorrect format) was submitted with the original supplement, but not with the subsequent amendments.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The label submitted in the January 22, 2009, amendment was compared to the label last approved

1 SPL was not submitted in correct format as required XML file

April 29, 2005. The proposed changes were correctly represented in the January 22, 2009 label. However, one additional change was found, but not annotated (underlined):

(b) (4)

Also, there was an error with the SPL submission. The sponsor submitted PDF and JPEG files rather than the required XML file type.

The content of the proposed changes is being reviewed by the clinical and clinical pharmacology reviewers.

Recommendations

This supplement is recommended for approval, pending other discipline review findings and further label negotiations with the sponsor. The above issues will be addressed in a communication to the sponsor that includes other various content revisions made by the review team. Because SPL was neither submitted properly in the original submission nor amendments, SPL will be requested at the time of approval.

Heather Buck, MS, MBA
Regulatory Project Manager

Supervisory Comment/Concurrence:

Cristi Stark, MS
Acting Chief, Project Management Staff

Drafted: HB 4/9/09
Revised/Initialed: CS 4/28/09
Finalized: HB 4/28/09
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Heather G Buck
4/28/2009 03:53:50 PM
CSO

Cristi Stark
4/29/2009 08:31:23 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021324Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Pediatric and Maternal Health Staff PMHS	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Heather Buck, OND/DGP (HFD-180), 301) 796-1413

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/16/09		21-324 S-008	prior-approval labeling supplement	10/29/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Entocort EC 3 MG capsules			4/15/09

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This is for a labeling supplement where the sponsor proposes to revise the Nursing Mothers sections in the [redacted] (b) (4) Precautions sections of the package insert (PI). We would appreciate any input regarding the proposed labeling changes. Specifically, we would like advice regarding the adequacy of advice to lactating women and the state of infant risk. The proposed changes are based on a study done in lactating women using an inhaled form of budesonide. See attached details. Submission can be found at: \\CDSESUB1\EVSPROD\NDA021324\021324.enx (note that the correct labels are in the 1/22/09 amendment).

SIGNATURE OF REQUESTOR Heather Buck 3/16/09	METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

PMHS Consult Request:

We have received a labeling supplement from the AstraZeneca. The Applicant is proposing to revise the "Nursing Mothers" sections in (b) (4) Precautions sections of the label for Entocort EC, an oral medication approved for the treatment and maintenance of remission of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. We would appreciate any input regarding the proposed labeling changes. Specifically, we would like advice regarding the adequacy of advice to lactating women and the state of infant risk. The Applicant is proposing these labeling changes based on a study done in lactating women using an inhaled form of budesonide.

Brief overview of study:

Astra Zeneca conducted a clinical pharmacology study (D5254C00763) to assess the concentration of budesonide in breast milk and estimate the exposure of to infants. This open-label, single center study was conducted in asthmatic women on maintenance treatment with Pulmicort Turbuhaler at dose levels of 200 or 400 μg twice daily. Eight mothers participated in the study. Plasma and milk samples were taken during the 8 hours after inhalation of budesonide. In addition, a single blood sample was taken from five of the eight infants for analysis of budesonide concentration.

Study Results:

In the lactating women, the mean maximal concentration of budesonide in plasma was 0.977 nmol/L in the 200 μg group and 1.714 nmol/L in the 400 μg group. The PK profile of budesonide in breast milk was also studied. The concentration of budesonide in milk was always lower than in plasma. The concentration of budesonide in five of the eight nursing infants was also measured. In all of the infants, budesonide plasma concentrations were below the lower limit of quantification (0.0500 nmol/L). Therefore, the plasma concentrations had to be estimated. Assuming 100% bioavailability, the infant budesonide plasma concentrations were estimated to be 600 times lower than in the mothers.

Previous studies have shown that oral budesonide, e.g. Entocort, has a higher bioavailability than inhaled budesonide (39% and 10-15%, respectively). However, because the total dose of oral budesonide in Entocort is higher than the inhaled budesonide dose in Pulmicort, the maximal plasma concentration of Entocort is expected to be higher. It is estimated that the concentration of budesonide found in breast milk after oral administration is 10 times higher than the maximal concentration found in the 400 μg bid group.

Proposed labeling:

(b) (4)

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/s/

Heather G Buck
3/16/2009 02:19:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: Nina Ton, OSE Project Manager

FROM: **Kristen Everett, Safety RPM, Division of Gastroenterology Products, 301-796-0453**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 2, 2009		21-324	SLR	10/29/2008; 1/22/2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Entocort			April 1, 2009

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☒ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Division of Gastroenterology products requests OSE to complete a review of the AERS database. We received a labeling supplement for Entocort EC (budesonide) capsules. The sponsor is proposing to include the term “anaphylactic reactions” in the Postmarketing Experience section of the label due to information from clinical study safety databases, external safety databases, regulatory safety databases, and the literature.

The sponsor’s search used Standardized MedDrA Query (SMQ) 20000021 terms: Anaphylactic reaction, Anaphylactic shock, Anaphylactic reaction, Anaphylactoid shock, Circulatory collapse, Shock, and Type I hypersensitivity. This search revealed two unique cases associated with the use of budesonide.

Known Previous events

Case 1: Anaphylactoid Reaction (Case ID 2003SE03422). The 23-year old female with Crohn’s disease reacted with tongue and throat swelling along with transpiration, wheezing, bowel complaints and diarrhea. Events occurred five minutes after the patient took the first capsule of Entocort. Subsequent, intracutaneous tests suggest a non-IgE mediated reaction. The patient’s previous history included an episode of buccal mucosa and lip swelling within 30 minutes of exposure to mesalamine.

Case 2: Circulatory Collapse (Case ID 1999AD00491). The patient experienced circulatory collapse one to two days after Entocort was discontinued. The circulatory collapse was part of a larger multi-organ failure.

We would like to know if there have been other reports of anaphylaxis associated with the use of budesonide. Currently, budesonide is the active ingredient in the following: Entocort, Entocort EC, Pulmicort Turbuhaler, Pulmicort Nebuamp, Pulmicort Respules, and Pulmicort Flexhaler.

We would like the search to focus on events of the SMQ 200000021 and adverse events associated with at least 2 of these 3 body systems:

a) Respiratory (upper or lower)
b) Dermatologic/Skin
c) Cardiovascular

The original SLR was submitted October 29, 2008; however, the sponsor updated the labeling in the January 22, 2009 submission. These submission can be found in the EDR under NDA 21-324.

Kristen Everett	METHOD OF DELIVERY (Check one) DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kristen Everett

2/2/2009 04:28:21 PM

Buck, Heather

From: Buck, Heather
Sent: Wednesday, January 21, 2009 2:09 PM
To: 'Kummeth, George'
Subject: RE: Entocort Capsules, NDA 21-324/S-008

Hello George,
Thanks for confirming. Actually, I thought I would summarize what I'm noticing with your electronic submission (below). It seems there are errors with every submission. Since the files you emailed me do not match those in the amendment, and since neither those in the amendment nor those emailed to me are correct, I propose the following. Submit another amendment summarizing the discrepancies I mention with the correct files. Feel free to give me a call or email me to discuss any of this. While I was able to confirm that the errors are on your side, there easily could be issues on our end as well. I am happy to work with you to ensure the correct files get reviewed.

0007 - Amendment - 1/13/09
annotated-draft-label.pdf - incorrect label submitted; label is for Symbicort
annotated-draft-label.doc - incorrect label submitted; label is for Symbicort
nonannotated-draft-label.pdf - Pulmicort Turbuhaler(R) in lowercase
nonannotated-draft-label.doc - Pulmicort Turbuhaler(R) in lowercase

Files emailed to me on 1/12/09
Annotated-draft-label.doc -
nonannotated-draft-label.doc - Pulmicort Turbuhaler(R) in lowercase

0006 - Labeling Supplement - 10/29/08
Incorrect date and code; should be Annual Report Amendment with letter date of 1/8/09

0005 - Labeling Supplement - 10/29/08
annotated-draft-label.pdf - Pulmicort Turbuhaler(R) in lowercase
nonannotated-draft-label.pdf - PULMICORT TURBUHALER(R) in UPPERCASE
nonannotated-draft-label.doc - PULMICORT TURBUHALER(R) in UPPERCASE; some changes are still tracked (if I were to accept, this file would be identical to
the nonannotated pdf file)

Regards,
Heather

-----Original Message-----
From: Kummeth, George [mailto:George.Kummeth@astrazeneca.com]
Sent: Wednesday, January 21, 2009 12:25 PM
To: Buck, Heather
Subject: RE: Entocort Capsules, NDA 21-324/S-008

Hello Heather,

Yes, I can conform that Pulmicort Turbuhaler should in fact be all caps.

Thanks for the catch. Regards, George

-----Original Message-----
From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Wednesday, January 21, 2009 10:19 AM
To: Kummeth, George
Subject: RE: Entocort Capsules, NDA 21-324/S-008

Hello George
I have another question. (b) (4)

(b) (4)

I noticed on nonannotated files submitted electronically, they are in all caps.
-Heather

-----Original Message-----
From: Kummeth, George [mailto:George.Kummeth@astrazeneca.com]
Sent: Monday, January 12, 2009 4:35 PM
To: Buck, Heather
Subject: Entocort Capsules, NDA 21-324/S-008

Hello Heather,

As we discussed, please find attached annotated and nonannotated Word versions of the Entocort Capsule labeling supplement, NDA 21-324/S-008. We will also submit these officially through the electronic gateway.

Thanks and best regards,

George

George A. Kummeth
Regulatory Affairs
AstraZeneca LP
302-885-8415

<<annotated-draft-label-jan122009.doc>>
<<nonannotated-draft-label-jan122009.doc>>

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/s/

Heather G Buck
1/21/2009 02:18:03 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-324/S-008 **PRIOR APPROVAL SUPPLEMENT**

AstraZeneca Pharmaceuticals LP
Attention: George A. Kummeth
Senior Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Kummeth:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ENTOCORT EC© (budesonide) Capsules.

NDA Number: NDA 21-324

Supplement number: S-008

This supplemental application proposes the following changes: Revisions to the prescribing information for ENTOCORT EC based on supporting documentation regarding Nursing Mothers and anaphylactic reactions.

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 December 26, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 29, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology 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 Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Heather G Buck

12/9/2008 08:35:57 AM