

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-324

MEDICAL REVIEW(S)

APPEARS THIS WAY
ON ORIGINAL

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS MEDICAL OFFICER'S REVIEW**

NDA: 21-324/AZ

Sponsor: AstraZeneca LP
725 Chesterbrook Blvd
Wayne, PA 19087-5677

Drug name: **ENTOCORT Capsules**

Dosage: 9 mg once daily

Route of Administration: Oral

Indication: The treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

Date submitted: August 2, 2001

Date received: August 2, 2001

Date assigned: August 7, 2001

Material Received: Sponsor's response to approvable letter dated July 24, 2001

Reviewer: Ruyi He, M.D.

1 BACKGROUND:

The original New Drug Application for Budesonide Capsules 3 mg was submitted to the FDA on January 24, 2001. The Agency's Approvable Letter was issued on July 24, 2001 for the indication of the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

In this submission, the sponsor submitted a complete response to the Agency's Approvable Letter with revised draft labeling and update safety information.

2 REVISED DRAFT LABELING

The revised draft labeling is identical to the labeling enclosed in the Approvable Letter, with one exception. The budesonide capsule identifier "CIR" is described in the "How Supplied" section of the draft labeling.

"CIR" represents "controlled ileal release". ENTOCORT capsules are not budesonide controlled ileal release capsules (FDA Bio-pharmaceutics Review for NDA 21-324) and "CIR" on ENTOCORT capsules is misleading to both physicians and patients. The Agency requested that the sponsor remove the identifier "CIR" from the budesonide capsule. The Agency also indicated that launch quantities with CIR on the capsule could be marketed in the U.S. for a period of 9 months following the teleconference dated July 23, 2001 to allow the company to complete the process of removing "CIR" identifier from the capsule (FDA Medical Officer's Review on NDA 21,324 BZ dated August 7, 2001).

Therefore, "CIR" in the "How Supplied" section is acceptable at this time. However, the sponsor must agree to update ENTOCORT labeling after 9 months from July 23, 2001 to remove "CIR" totally from the ENTOCORT labeling.

3 SAFETY UPDATE

This Safety Update Report (SUR) covers the timeframe of January 1, 2001 through June 30, 2001, and contains the following:

- An update of all deaths and serious adverse events from ongoing ENTOCORT clinical trials received by AZ during the reporting period
- Copies of all Clinical Study Reports completed during the reporting period. This includes an interim report for an ongoing pharmacokinetic study in pediatric and adult patients (Study No. 08-3044; total of 13 subjects) and a final report for a clinical study in pediatric patients (Study No. 08-3037; total of 48 subjects)
- An update of postmarketing reports received by AZ during the reporting period.
- An updated review of the published literature during the reporting period

3.1 Deaths and Serious Adverse Events during Clinical Studies

No Serious Adverse Events or deaths occurred in clinical trials during the Safety Update Reporting period of January 1, 2001 through June 30, 2001

3.2 Completed Clinical Studies

There were 11 ongoing studies as of the last Safety Update Report. Only 1 of the studies has had a completed study report issued during the Safety Update reporting period, Study

SD-008-3037, "Efficacy and Safety of ENTOCORT Capsules versus Prednisolone in Children with Active CD/ Randomized, Double-blind with Two Parallel Groups".

Study SD-008-3037 was terminated prematurely due to increasingly poor recruitment rate. The goal of 120 patients was not reached within 18 months and the sponsor decided to terminate the study. A total of 48 patients was randomized in this study, 33 (69%) were males and 15 (31%) were females. Their average age was 12.8 (range 8-16) years. All but 4 were Caucasians. The patients had had their disease under study diagnosed for a median time of 0 (range 0-6) years. A total of 30 patients (14 in the Budesonide group and 16 in the Prednisolone group) completed the study.

Efficacy results of Study SD-008-3037: Within 2 weeks 50% of the patients had gone into remission ($CDAI \leq 150$) with budesonide or prednisolone. After 8 weeks treatment, 55% of patients in the budesonide group were in remission compared with 71% in the prednisolone group. Because of the small size of the two treatment groups, no conclusion can be made. The present data suggest that with the dosing regimen used in this study, there was a somewhat higher efficacy with prednisolone than with budesonide.

Safety results of Study SD-008-3037: Prednisolone had a considerably stronger suppressing effect than budesonide on the HPA-axis. During the initial four weeks of the trial, when the highest dose of prednisolone was given, only 10% of the children had plasma cortisol of at least 150 nmol/L (the lower normal limit). The corresponding percentages during the 8-week period when budesonide 9 mg was given varied between 37% and 58%. The difference in percentage of patients with abnormal morning P-cortisol was close to significant ($p = 0.052$). The quantitative difference in morning P-cortisol was highly significant in favour of budesonide ($p = 0.0028$). In agreement with the effect on the HPA-axis, hypercorticism, particularly appearing as moon-face or acne, was considerably more frequent among the prednisolone treated children. Second to endocrine disorders, gastrointestinal AEs (mainly caused by the underlying disease) were most common in the two treatment groups. Beside relatively strong suppression of the HPA-axis function, particularly with prednisolone, the present data have not revealed any findings in children that were not known from studies in adults with Crohn's disease.

For one of the ongoing studies, Study 08-3044, "Pharmacokinetics of ENTOCORT Capsules in Children and Adults with CD / Open Label", a second interim report was issued during the reporting period of this Safety Update Report. The few reported adverse events in this study were mainly related to the underlying disease or isolated symptoms. There were no serious adverse events or discontinuations due to adverse events reported during the study. No clinically important safety related findings were identified.

3.3 Post-marketing Experience

Serious and Non-serious Post-marketing Adverse Events

In total 5 SAE cases (which include 9 AEs) and 4 non-serious cases (which include 7 AEs) have been reported from the worldwide marketed use of ENTOCORT during the

reporting period of this Safety Update, i.e. received January 1, 2001 through June 30, 2001. Table 1 summarizes the 9 cases.

TABLE 1
Post-marketing Surveillance of ENTOCORT
January 1, 2001 through June 30, 2001

Safety Database Identification Number	Country	MedDRA Preferred Term	Serious Y/N	Reporter Assessment of Causality	Outcome
2001UW04704	United States	Menstrual Disorder NOS	N	related	not yet recovered
2001SE03353	Australia	Pierre Robin Syndrome*	Y	possible	unknown
2001SE02292	Sweden	Sepsis NOS*	Y	possible	recovered without sequelae
2001SE01206	United Kingdom	Abdominal Pain Upper	N	not reported	unknown
2001SE01070	France	Interstitial Lung Disease* Hypertension NOS; Edema lower limbs; Face edema	Y N N N	possible	unknown
2001CG00808	France	Abdominal Pain Lower	N	possible	improved
2001CG00557	France	Blood Potassium Decreased	Y	possible	unknown
2001CG00209	France	Medication Error* Leukocytosis, NOS	Y N/A	probable	recovered without sequelae
2001AP03032**	United Kingdom	Visual Acuity Reduced*; Dementia NOS*; Balance Impaired NOS*; Vision Blurred.	N N N N	not reported	unknown
Y/N Yes or No N/A Not available * MedDRA Preferred terms not listed in the adverse reaction section of the PI considered approvable by the Agency as of July 24, 2001 ** Consumer report not medically substantiated					

One of the SAE cases, 2001SE03353, reports a congenital birth defect in an infant whose mother took both budesonide and mesalazine during pregnancy. There were no deaths reported during the reporting period.

3.4 Review of Published Literature

A search of MEDLINE, EMBASE, BIOSIS, SCISEARCH and the AstraZeneca database PLANET by the sponsor yielded one article updating the information on three cases of benign intracranial hypertension in adolescents who were taking budesonide for Crohn's Disease. Manufacturer's report numbers are 2000UW05280, 2000LJW05282 and

2000UW05283. The full-text article revealed that the suspect drug was Budenofalk (budesonide) rather than Entocort (budesonide). The information on these 3 cases of benign intracranial hypertension in adolescents who were taking budesonide for Crohn's Disease, has been updated in Entocort labeling by the Agency as of July 24, 2001.

3.5 Summary of Safety Update

This safety update covers the period January 1, 2001 – June 30, 2001. The 9 post-marketing cases with severe adverse events, 1 report of exposure during pregnancy delivered an infant with Pierre Robin Syndrome and a literature article updating the information about 3 cases of benign intracranial hypertension with budesonide, are all included in this safety report. Review of these update data does not provide new evidence that requires an update to the safety profile of Entocort.

4 CONCLUSION

In this submission, the sponsor submitted a complete response to the Agency's Approvable Letter dated July 24, 2001 with revised draft labeling and update safety information.

Revised draft labeling with "CIR" in the "How Supplied" section is acceptable at this time. However, the sponsor must agree to update ENTOCORT labeling after 9 months from July 23, 2001 to remove "CIR" totally from the ENTOCORT labeling. Review of Safety Update does not provide new evidence that requires an update to the safety profile of Entocort.

Ruyi He, MD

CC:
NDA 21-324/AZ
HFD-180/Div. Files
HFD-180/L. Talarico
HFD-180/J. Korvick
HFD-180/H. Gallo-Torres
HFD-180/R. He
HFD-180/L. Zhou
HFD-180/J. Choudary
HFD-181/M. McNeil
f/t 9/6/01 rh

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/s/

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Lilia Talarico
9/21/01 10:52:05 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS MEDICAL OFFICER'S REVIEW**

NDA: 21-324/N-000-BZ Proposal for interim use of capsule identifier "CIR"

Sponsor: AstraZeneca LP
725 Chesterbrook Blvd
Wayne, PA 19087-5677

Drug name: **ENTOCORT Capsules**

Dosage: 9 mg once daily

Route of Administration: Oral

Indication: The treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

Date submitted: July 30, 2001

Date received: July 31, 2001

Date assigned: August 2, 2001

Material Received: Sponsor's request for extension of time needed to remove "CIR" identifier from the ENTOCORT capsule from 6 to 9 months

Reviewer: Ruyi He, M.D.

BACKGROUND:

The original New Drug Application for Budesonide Capsules 3 mg was submitted to the FDA on January 24, 2001. The Agency's Approvable Letter was issued on July 24, 2001 for the indication of the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

A teleconference was held on Monday July 23, 2001 with representatives from AstraZeneca and in discussions the Agency requested the Sponsor to remove the identifier "CIR" ("controlled ileal release" an identifier used in Europe) from the budesonide capsule. The Agency indicated that launch quantities with CIR on the capsule, could be marketed in the U.S. for a period of time following approval. The Agency offered 6 months as a reasonable time period to allow the company to complete the process of removing this identifier from the capsule. In this submission, the sponsor

requests a minimum 9 months for implementation of this change.

JUSTIFICATION:

In justifying the request the sponsor provides the following information:

This is a low volume product and manufacturing campaigns need to supply all markets, removal of the capsule identifier "CIR" would need to be implemented worldwide in order not to be cost prohibitive. A reasonable amount of time to accomplish this would be 12 months; however, at a minimum, 9 months would be required to allow for implementation of this change through AZ suppliers, manufacturing operations and supply chain, and would require the following:

- Create a new product image with capsule supplier
- Produce new excipient specifications (empty hard gelatin capsules)
- Produce product specifications, test methods and packaging specifications
- Change Global purchasing procedures
- Order and stock additional components for manufacturing
- Perform validation of the new capsules
- Manufacture, test, release and package new batches with a new capsule image
- Revise labeling worldwide and notify non-US Regulatory Authorities.

The sponsor commits to the Agency that AZ will not use the CIR markings in any way to imply delayed- or extended-release of budesonide from the drug product.

REVIEWER'S COMMENTS AND RECOMMENDATIONS

The Agency requested that the Sponsor remove the identifier "CIR" from the budesonide capsule. However, the Agency indicated that launch quantities with CIR on the capsule could be marketed in the U.S. for a period of 6 months following the teleconference to allow the company to complete the process of removing "CIR" identifier from the capsule. In this submission, AZ requests a minimum 9 months for implementation of this change.

"CIR" represents "controlled ileal release". ENTOCORT capsules are not budesonide controlled ileal release capsules (FDA Bio-pharmaceutics Review for NDA 21-324) and "CIR" on ENTOCORT capsules is misleading to both physicians and patients. Therefore, the time to allow the ENTOCORT capsules marked by CIR on the market should be as short as possible. The sponsor should start the process immediately after the teleconference on July 23, 2001 for the change and it is no reason to wait after approval.

The sponsor has provided a reasonable support for the request. I recommend that 9 months from July 23, 2001 to allow the company to complete the process of removing "CIR" identifier from the ENTOCORT capsules.

The recommendations should be communicated to the sponsor.

Ruyi He, MD

CC:

NDA 21-324/N-000-BZ

HFD-180/Div. Files

HFD-180/L. Talarico

HFD-180/J. Korvick

HFD-180/H. Gallo-Torres

HFD-180/R. He

HFD-180/L. Zhou

HFD-180/J. Choudary

HFD-181/M. McNeil

f/t 8/07/01 rh

N21324-0000BZ/RH

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/s/

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**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 4, 2001

FROM: Medical Team Leader
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: NDA 21-324
ENTOCORT (budesonide) capsule
(AstraZeneca LP)

TO: Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Crohn's disease (CDz; regional enteritis)¹ is a chronic granulomatous disease, which may occur anywhere in the gastrointestinal tract from the mouth to the anus. The ileum most often is involved, with more than 50% of CDz patients having **ileocolitis**. The **etiology** of CDz is unknown, but genetic² and infectious³ agents appear to play a role; an altered **immunologic mechanism** presently is the most prominent theory: abnormal numbers, subsets and functions of T cells have been identified. A mycobacterium (*M. paratuberculosis*)⁴ has been proposed as an etiologic agent.

Clinical manifestations are characterized by periodic exacerbations and remissions. **Clinical features** include pain (often colicky, especially in the lower abdomen), diarrhea (usually the presenting symptom), systemic symptoms (including fever, weight loss, malaise and anorexia), fistulae (to the skin or other organs, occurring in ca. 20% of patients), perianal fistulae or abscesses (especially common in Crohn's colitis) and numerous extra intestinal manifestations [anemia; fatty liver, pericholangitis, nonspecific hepatitis, cirrhosis, sclerosing cholangitis⁵; renal disorders⁶, peripheral arthritis (noted in

¹ The first peak of incidence occurs between the ages of 12 and 30y; a second peak occurs at age 50y.

² An increased incidence of disease has been noted in monozygotic twins and siblings. In comparison to the general population, Jewish men have 6 times the risk of developing CDz.

³ Infectious agents have been postulated but never identified as a cause of CDz. Bacterial flora is considered to play a central role in inflammatory bowel disease [CCFA: Interactions Between Genetics and Microbiology in Inflammatory Bowel Disease. The Westin Resort, Hilton Head, South Carolina, March 2-5 (1995)].

⁴ [Proposed by David Y. Graham (VA Medical Center, Houston) and other investigators]

⁵ [There is an increased incidence of gallstones. Liver enzymes or liver biopsy abnormalities are noted in 50 to 70% of CDz patients]

⁶ [Including right ureteral obstruction secondary to contiguous bowel involvement and nephrolithiasis. An increase in Ca oxalate stones is due to increased oxalate absorption and an increase in uric acid stones is ascribed to increased cell turnover and a concentrated acid urine]

10% to 12% of patients) and ankylosing spondylitis (noted in 2% to 10% of patients); skin problems⁷; episcleritis or uveitis (which may occur in 3% to 10% of patients)]. **Therapy of CDz** is symptomatic. Neither specific therapy nor cure exists. The goals of medical therapy are to suppress the inflammatory response, allow healing of tissue and relieve the symptoms of fever, diarrhea, and abdominal pain. Surgery may be necessary for recurrent intestinal obstruction, enterocutaneous fistulae, and perforation and for growth retardation that does not respond to increased caloric intake⁸.

Agents currently used in treatment of CDz vary widely in their applications and adverse events. Based on their mechanism of action on the pathogenesis of the disease, these can be grouped as summarized below.

**Range of Therapeutic Approached Based on Pathogenesis
IBD Therapy**

	<u>Ex of Drugs</u>
1. Antigen processing and presentation. Macrophage activation	Antibiotics Probiotics
2. Antigen recognition and Activation of CD ₄ + T cells	AZA/6MP CyA ?MTX Tacrolimus
3. Generation of TH1/TH2 response	IL-10
4. Production of proinflammatory cytokines	Anti-TNF Antibodies (Infliximab) Thalidomide Corticosteroids IL-11
5. Recruitment, migration and adhesion	Antisense oligonucleotide to ICAM-1 Anti-X 4 integrin antibody ? Heparin
6. Inflammation and injury	Aminosalicylates Corticosteroids ? Local anesthetics
7. Repair and restitution	? Heparin ? IL-11 ? Nicotine

Hugo E. Gallo-Torres: Presented at the July 7-12, 2001 DIA meeting, Denver, Colorado

⁷ [These include erythema nodosum and, rarely, pyoderma gangrenosum].

⁸ [The recurrence rate after initial resection may be as high as 80% within 15y].

It is worth noting that only a few of the above listed agents have been approved by the FDA for Crohn's-related indications. **Corticosteroids** have been a mainstay of the acute treatment of CDz for many years. But conventional corticosteroid therapy has many drawbacks, including a wide range of commonly recognized side effects, particularly with high doses and/or prolonged use.⁹ Nonetheless only corticosteroids and infliximab are FDA approved for the indication being sought by the sponsor. The efficacy of corticosteroids in managing acute CDz has been well established in a number of reviews and meta-analyses.¹⁰ Infliximab is the first example of a biological response modifier used in the treatment of CDz. Infliximab is a chimeric monoclonal IgG1 antibody against TNF. The antibody neutralizes TNF and effectively clears it.¹¹

There are three possible main indications: a) treatment of CDz; b) induction of remission and c) maintenance of remission. Of these, the indication for **budesonide (ENTOCORT)** being sought by the sponsor is:

Proposed indication: treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

Budesonide (16 α , 17 α -butylidenedioxypregna-1,4-diene-11 β , 21-diol-3, 20-dione) is a glucocorticosteroid. The highlights in the present secondary review of NDA 21-324 are based on primary reviews from the following disciplines: Chemistry (Dr. R. P. Frankewich), Pharmacology/Toxicology (Dr. Sushanta Chakder), Clinical Pharmacology and Biopharmaceutics (Dr. Sandip K. Roy), Statistics (Dr. Sue-Jane Wang, with a secondary review on Statistics by Dr. T. Permutt), Medical (Dr. Ruyi He), DDMAC-Advertising (Ms. Margie Kober) and DDMAC-QOL (Dr. L. Burke).

Classic corticosteroids continue to be appropriate for use in some patients with active disease. At pharmacological doses, the biological effects of corticosteroids, both beneficial and deleterious, are numerous; they profoundly affect both immunologic and inflammatory responses. Corticosteroids diminish production of a host of proinflammatory cytokines and directly inhibit a variety of leukocyte functions, including adherence, chemotaxis, and phagocytosis, and interfere with metabolism of arachidonic acid and production of eicosanoids. Drugs may be administered orally, intravenously in severe disease, or rectally for topical therapy in distal colitis. In CDz, a substantial number of patients are unable to discontinue therapy without recurrent symptoms,

⁹ [In a recent publication, M. Robinson, Optimizing Therapy for Inflammatory Bowel Disease, Amer. J. Gastroenterology 92:125-175 (1997), states: "In fact the disadvantages of corticosteroid therapy are so impressive that these agents might not be approved for therapeutic use if they were now in clinical trials".]

¹⁰ [P. Salomon et al. How effective are current drugs for Crohn's Disease? A meta-analysis. J. Clin. Gastroenterol. 14: 211-215 (1992)].

¹¹ [S.A. Siegel et al. The mouse/human chimeric monoclonal antibody cA₂ neutralizes TNF in vitro and protects transgenic mice from cachexia and TNF lethality in vivo. Cytokine 7: 251-259 (1995)]

[As in IgG1, it may also effect cell lysis through complement fixation or antibody-dependent cell-mediated cytotoxicity: (ADCC)]

whereas others fail to respond altogether. To meet this medical need, **novel corticosteroids**, such as budesonide with high potency and low bioavailability have been developed to minimize the adverse systemic consequences of classic corticosteroids, although they may not improve in either short- or long-term efficacy.

I. CHEMISTRY

According to the July 10, 2001 CMC review, the application may be approved with the following recommendations:

- The notation "CIR" (for "Controlled Ileal Release") be removed from the gelatin capsules, and all references to it be removed from the applicant's raw material specifications for them, since concerns exist about the release mechanism of the drug product (CMC Review #1 pg. 19, and also CPB review for this NDA).
- Expiration date of the drug product, in the packages proposed for market, should be 18 months (point no. 19 of CMC review).
- The labeling comments in CMC Review #1 is considered.

The composition of the hard gelatin capsules is provided in Table 15 on pg. 004-001-058 of vol. 1.3 of NDA 21-324. Assurance has been provided that all components meet appropriate compendial or CFR requirements:

Inactive Ingredient		Compendial Reference
Capsugel	Shionogi	
Gelatin	Gelatin	NF
		21 CFR 73.1200
		21 CFR 73.1200
		21 CFR 73.1200
Titanium oxide	Titanium oxide	USP

All of the Drug Master Files (DMFs) listed under SUPPORTING DOCUMENTS in the CMC Review have been reviewed. Information request letters are being sent to the holders of DMFs

II. PHARMACOLOGY/TOXICOLOGY

(Review dated June 25, 2001).

From a preclinical standpoint, the NDA application is approvable.

Included were reviews on pharmacology, ADME, acute toxicity (rat: oral, S.C.; mouse: oral, S.C.), subacute/subchronic/chronic toxicity (rat, dog, rabbit, monkey), reproductive toxicity (segments I, II, and III), carcinogenicity studies (mouse: 91-week, drinking water; rat: 104-week, drinking water and another 104-week, drinking water in male rats), and a battery of mutagenicity studies. Also incorporated were reviews of studies submitted as part of NDA 20-333 for Rhinocort Nasal Inhaler (HFD-570), reviewed by Dr. Conrad Chen and studies submitted as part of _____ for CIR capsules and a series of new studies.¹²

Summary findings on pharmacology/toxicology are reflected in the budesonide proposed draft labeling. In summary, oral bioavailability of budesonide from the CIR capsules is very limited; only 0.9 to 1.4% of the administered dose is available in monkeys. Most of the adverse effects observed in preclinical toxicology studies (such as gastric ulcerations, atrophy of the thymus, spleen, lymph nodes and adrenal glands, decreased WBC levels and decreased plasma cortisol levels) are related to the glucocorticoid activity of the compound. The pharm/tox reviewer indicates that although budesonide had typical glucocorticoid side effects they were milder as compared with other glucocorticoids. In rats, while prednisolone and dexamethasone caused reductions of the thymus weights or the number of T-cells in the thymus, budesonide had no effect on the thymus. Budesonide was 0.1 times less effective than beclomethasone in suppressing the stress-induced increase in the plasma cortisol levels in guinea pigs. The pharm/tox reviewer concluded that the sponsor has a) adequately characterized budesonide and b) conducted sufficient preclinical oral and subcutaneous toxicity studies in different species.

III. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

(Reviews dated July 2, 2001)

Recommendation: Clinical Pharmacology and Biopharmaceutics information submitted under this NDA is acceptable from OCPB perspective.

The following synopsis was taken from Dr. Sandip K. Roy's review.

The sponsor described the dosage form as a modified release capsule. The reviewer concluded that ENTOCORT is a **prolonged-release** capsule of budesonide, consisting of small pellets <1.4 mm in diameter. The pellets are designed to resist the gastric juice and to continuously release budesonide during passage through the small intestine and the

¹² These included published pharmacology studies on budesonide, its covalent binding in liver and brain from male rats, irreversible binding of the drug and other steroids to liver and brain from rats, *in vitro* formation and degradation of 21-aldehydes of budesonide and cortisol in liver preparations from human, rat and mouse, *in vitro* metabolism of budesonide epimers in the male and female rat liver and brain, and exploratory mutagenicity studies of 21-aldehyde of budesonide, related glucocorticoids and other keto aldehydes.

ascending colon. The site of uptake of budesonide was studied using the technique of gamma scintigraphy. The transit of the pellets through the GI tract was followed up to 72 h, using ^{111}In -labeled pellets as a tracer. The sponsor relied on this method in several studies to estimate that 40 to 70% of the dose was absorbed in the ileum and ascending colon. However, in this method, ^{111}In pellets were assumed to have the same transit time through the GI tract as budesonide CIR pellets. No rationale was provided in support of this assumption.

- In a study conducted with eight ileostomy-operated subjects, the use of ileostomy pouches in the participating subjects offered a possibility to collect non-absorbed budesonide after passage through the small intestine. The cumulative amounts of budesonide obtained in the effluent were approximately 6 times higher when budesonide was given as CIR compared to plain capsules. These data only indicated that the release of budesonide from CIR formulation is delayed and/or prolonged compared to micronized budesonide in plain capsules. Entocort capsule **did not exhibit delayed release characteristics in a consistent manner** and the dosage formulation does not appear to be reliable. These findings were discussed at a July 3, 2001 Biopharm meeting. It was concluded that these and other data summarized below were not approvability matters and that the labeling should describe the characteristics of the formulation in detail.
- In study 08-3015, there was no difference in C_{max} and T_{max} between plain and CIR capsules. T_{max} values ranged between 30 and 360 minutes for budesonide CIR capsules.
- In another study (08-3019), only at higher doses and in fewer subjects, the formulation exhibited delayed release characteristics whereas in others it behaved like an **immediate release formulation**. Individual T_{max} values varied between 1.5 to 6.0 h.
- Safety data were collected as plasma and urinary cortisol suppression, which is a marker of HPA axis function. Extent of cortisol suppression often correlated well with PK parameters. Dose adjustment in the label was recommended based on safety concerns arising from increase in systemic exposure in subjects with hepatic impairment and due to factors that influence metabolism (CYP3A inhibition) and release (increase in pH).

In addition, the Clinical Pharmacologist Reviewer recommended that the following two statements be sent to the sponsor:

- ◆ The granules in ENTOCORT capsules were stated to provide gastro-resistant, delayed and extended release properties to the formulation. However, the data show that the product does not exhibit these characteristics in a consistent manner. In study 08-3015, three out of twelve (25%) subjects had T_{max} values equal to or shorter than 60 minutes. Three other subjects had T_{max} values of 120 min. In addition, there was no difference in C_{max} and T_{max} between plain and CIR capsules. In another study

(08-3019), at both 3 and 9 mg doses seven out of 12 subjects (58%) had T_{max} values of about 1.5 h.

- ◆ In the method used to study the site of uptake of budesonide, no rationale was provided in support of the assumption that ^{111}In pellets will have the same transit time through the GI tract as budesonide CIR pellets. Furthermore, if the enteric coating is set to dissolve at $\text{pH} > 5.5$, it is not likely that delayed release will last until the ileum. The Biopharm Reviewer notes that there are published data in fasting subjects indicating pH in stomach and duodenum at 5.5. This 5.5 pH is higher than the usual pH 1 to 2 found in many fasting individuals. The pH changes after ingestion of food may go down, or upon passage into the duodenum, where the pH because of the contribution of the biliary/pancreatic secretions is usually higher.

There is also the issue of **Control Ileal Release (CIR)**, a European nomenclature. As discussed above, the formulation does not consistently release the medication in the terminal ileum. But even if this were indeed demonstrated, the usefulness of the formulation would be limited because, although CDz many times begins at the terminal ileum, the condition usually progresses to more proximal areas of the ileum so that release of the medication in the upper ileum as well as the jejunum and duodenum may be needed. This MTL agrees with the Biopharm recommendation that, since the formulation has proven efficacious in the clinical trials, it is best to succinctly describe what happens to it (the formulation) while in the alimentary canal without trying to characterize it by a specific (inaccurate) name.

IV. MEDICAL/STATISTICS

Based on Dr. He's Medical review, the Statistical review and evaluation from Dr. Sue-Jane Wang and the secondary review by Dr. T. Permutt, NDA 21-324 for ENTOCORT (budesonide) capsules is **approvable**.

As detailed in the above reviews, the clinical program in NDA 21-324 consisted of 5 randomized, multi-center, double-blind, placebo- or active-controlled trials. All in all, except for the comments included below, the 5 trials were well-designed and apparently well-executed. The study population was well defined and consisted of patients with mild to moderate CDz involving the ileum and/or ascending colon. The major inclusion criteria were adult CDz patients who provided informed consent. Exclusion criteria were adequate for this type of study. Active CDz was shown by means of the Crohn's Disease Activity Index (CDAI) score between 200 and 450. Either X-ray, endoscopy or histology was used to demonstrate that the disease was limited to the ileum, cecum and/or ascending colon. The CDAI was the main clinical assessment used for determining drug efficacy. Although not ideal, the CDAI provides a reasonably standardized index for measuring disease activity and it is an accepted standard for use in CDz clinical trials. The following variables were considered in calculating the CDAI:

1. Number of liquid or very soft stools per day (derived from patient diary).
2. Abdominal pain rating (none, mild, moderate, severe derived from patient diary).
3. General well-being rating (generally well, slightly under par, poor, very poor, terrible) (derived from patient diary).
4. Existence of complications, including arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum or aphthous stomatitis; anal fissure, fistula or abscess; other fistula; fever over 37.8°C (100°C) during past week (derived from clinical examination).
5. Use of diphenoxylate, loperamide or other opioids for diarrhea (derived from patient diary and elicited during clinical examination).
6. Presence of abdominal mass (absent, questionable, definite) (derived from clinical examination).
7. Body weight (derived from clinical examination).
8. Hematocrit value (derived from blood sample).

In each trial, calculation of the CDAI was done at the randomization visit and at each subsequent follow-up visit. As shown above, certain components of the CDAI were derived from a daily patient diary and reflected activity over the previous 7-day period.

Primary/Secondary Efficacy Endpoints

In each of the 5 trials, the main efficacy endpoint was the proportion of patients in each treatment group demonstrating **clinical improvement**. It is important to point out that, although in the sponsor's Clinical Report, the phrase "induction of remission" is used in many instances, the ENTOCORT trials **did not assess induction of remission**. Clinical improvement was defined as a CDAI score of ≤ 150 at the end of 8 weeks. In the study protocols and reports, a CDAI score of ≤ 150 was defined (by the sponsor) as disease remission. However, as clearly stated in the MOR review, this clinical endpoint is better defined as indicative of **clinical improvement**.

For completeness, the definitions of the three possible indications are as follows: (Taken from the Draft Guidelines "Clinical Evaluation of Drugs for Crohn's Disease"):

A. Treatment of Acute Disease

[The indication requested by the sponsor]

Defined as symptom and sign reduction. If symptoms alone improve, this should be reflected in the claim. The indication could be based on improvement in specific, pre-specified symptoms or conglomerate symptom complex.

B. Induction of Remission

[Not the indication requested or to be granted for budesonide]

Defined as resolution of symptoms and signs and documentation of mucosal healing. Relief of symptoms alone, unless complete (in the absence of mucosal healing) is unreliable of response. Luminal narrowing, in the absence of mucosal ulceration will not preclude the remission indication. Histological confirmation is not required.

C. Maintenance of Remission

[Not the indication requested or to be granted for budesonide]

Defined as absence of symptoms, mucosal features of acute inflammation. Symptomatic remission, if demonstrated, may form the basis of claim limited to findings. Chronic mucosal changes such as distortion of the submucosal vasculature, erythema or post-inflammatory pseudo-polyps may persist without ulceration.

Comments on Clinical Trials

For two of the five trials (Studies 08-3001 and 08-3025), it was specified that the proportion of patients with clinical improvement at Week 8 was the primary endpoint of interest. Although a primary time point was not specified for the other three studies (08-3002, 08-3013 and 08-3027), they did include an 8-week evaluation.

Secondary efficacy endpoints varied from trial to trial and included: a) Time to response (defined as the first follow-up visit where a CDAI score of ≤ 150 was recorded); b) Mean value and mean change from baseline in total CDAI score at each post-randomization visit; c) Quantitative change in each component of the CDAI score at each post-randomization visit; d) Proportion of patients demonstrating a therapeutic benefit, defined as a CDAI score of ≤ 150 or a decrease from baseline in CDAI of ≥ 100 , at each follow-up visit; e) Physician's global evaluation; and f) Quality of life assessment. Information from these secondary efficacy endpoints are discussed in detail in the individual trial appraisal by the MOR. These data are not discussed here.

The specific statistical methods used to analyze efficacy variables in each trial are summarized in Table 7 of the MOR. When applicable statistician's comments related to the individual trials, are mentioned below.

Is it to be noted that the main purpose of the sponsor's clinical program was to demonstrate that, owing to its pharmacological properties (novel, **poorly absorbed** corticosteroid), budesonide is a safer drug than classic corticosteroids (i. e. prednisolone). Accompanying these safety claims was a demonstration that budesonide was active when

compared to placebo but not necessarily “superior” to active comparators. The 5 clinical trials included: a) a comparison to mesalamine (08-3027); b) two placebo-controlled studies (08-3001 and 08-3025) and two comparisons to prednisolone (08-3013 and 08-3002).

Results of Efficacy Evaluations

a. Mesalamine-controlled Trial (08-3027)

In this study, ENTOCORT 9 mg q.d. was statistically significantly better than mesalamine (2 g/b.i.d.) in inducing clinical improvement (68% vs 42%,) at 8 weeks, with a clinically meaningful therapeutic gain (24%) (p = 0.001).

The statistician reviewer (p. 18) points out that in this study, 83% (77/93) of budesonide-treated patients completed the 16-week study which was higher than the 56% (50/89) among those treated with mesalamine. As shown in the Table below, the proportion of patients who dropped out early in the trial was 2.6-fold higher with mesalamine (44%) than with budesonide (17%). The major reasons for these higher mesalamine discontinuations were serious AEs (9% vs 3%) and treatment failure (30% vs 11%).

Study 08-3027
Proportion of Patients (%)

	Who Completed the Trial	Who Dropped Out	Who Experience SAE	With Treatment Failure
Mesalamine (2 g b.i.d.) [n=89]	56	44	9	30
Budesonide (9 mg qd) [n=93]	83	17	3	11

Extracted from Table 3 of sponsor's 008-068-050; modified by the MTL

Mesalamine is not an approved drug for CDz and there may be some doubt as to its effectiveness. As pointed out by the STL, however, unless mesalamine is worse than nothing, a drug that is better than mesalamine must be effective. Actually, the results of study 08-3027 suggest — although they do not prove — that budesonide is not only more effective but it may also be better tolerated than mesalamine.

b. Placebo-controlled trials (08-3001 and 08-3025)

Study 08-3001 showed that ENTOCORT 4.5 mg b.i.d. was statistically significantly better (50% vs 20%) in inducing clinical improvement of active CDz with a clinically meaningful therapeutic gain of 31% at 8 weeks. This study consisted of 4 arms: the two additional arms were budesonide 3 mg (1.5 mg b.i.d.), the other budesonide 15 mg (7.5 mg b.i.d.). As shown in the Table below, in this study, a difference in dropout rate was seen between the budesonide 4.5 mg b.i.d. and placebo. The primary reason for treatment discontinuation was treatment failure.

Study 08-3001

Proportion of Patients Who	PL [n=66]	Budesonide (mg b.i.d.)		
		1.5 [n=67]	4.5 [n=61]	7.5 [n=64]
• Dropped out (%)	58	54	31	41
• Dropped out and had disease deterioration (%)	48	45	26	28

Extracted from Table 3 of sponsor's 008-008-082; modified by the MTL

The regimen of budesonide shown to be effective in study 08-3001, 4.5 mg b.i.d. was not the regimen that is proposed to recommend (9 mg qd).

As mentioned by the STL, it would naturally have been preferable to test the 9 mg q.d. regimen. However, as shown below, in the two trials in which the two 9 mg q.d. regimens were compared, 3013 and 3025, the single and divided doses were not much different in placebo-comparison 3025 and the single daily dose was better in study 3013. Efficacy of the divided doses in study 3001, therefore, strongly suggests that 9 mg q.d. would also have been effective. The MTL agrees with Dr. He that study 3001 is considered supportive.

In study 3025, there were 2 budesonide treatment arms (9 mg q.d., n=79 and 4.5 mg b.i.d., n=78) and a placebo arm (n=41). This study failed to show a statistically significant effect by the primary analysis. But, according to Dr. Permutt, this analysis was an inappropriately insensitive omnibus test for any differences among ENTOCORT 9 mg q.d., ENTOCORT 4.5 mg b.i.d., and placebo, whereas clearly the important contrast is between placebo on the one hand and the two ENTOCORT regimens on the other. In fact, both these regimens were substantially better than placebo numerically (therapeutic gains of 15% and 20%, respectively) and not much different from each other: 52% remission at 8 weeks for ENTOCORT 4.5 mg b.i.d., 48% for ENTOCORT 9 mg q.d.; both of these were higher than the 32% for placebo. Dr. Permutt further comments that although the primary analyses were not ideal, it would have been acceptable if they had succeeded. So, to prefer another analysis after the fact would raise questions of multiplicity. I agree with the STL that study 3025 cannot therefore be said to add significantly to the findings of other studies. It is substantially consistent with them, however, and so does not take anything away, either. In addition, the MOR, speculates that the lack of statistically significant difference (by primary efficacy analysis) might be due to a) less patients randomized to the placebo arm (2:1 enrollment, n=41), and b) more patients with mild disease (CDAI <300) enrolled (71%) in comparison with the (other) placebo arm in study 3001 (62%). Also, a significantly less proportion of male patients in the 9 mg q.d. group (23%, 19/61) than in the other two arms (44% and 44%) was enrolled, although, across the group, less male, than female patients were enrolled in the trial. Finally, time since resection in the 9 mg q.d. arm (6.9y) was significantly longer than the other two arms (3.2 and 2.9y, respectively). In reality, it is not known if these imbalances might have influenced the trial results.

c. Prednisolone-controlled trials (08-3002 and 08-3013)

As pointed out in the MOR, after 8 weeks of treatment randomization, clinical improvement rates of 60% were seen with ENTOCORT 9 mg q.d. and prednisolone in study 3013 while there was a 13% less clinical improvement rate (52%) in the ENTOCORT 9 mg q.d. than in the prednisolone arm in study 3002. However, this difference was not statistically significant ($p=0.12$). **Non-inferiority comparisons are difficult because the protocol did not specify a non-inferiority margin.**

The statistician calculated upper confidence bounds for the inferiority (if any) of ENTOCORT 9 mg q.d. to prednisolone were 27% for study 3002 and 18% for study 3013. These post-hoc analyses suggest — but do not prove — that budesonide might be less effective than prednisolone. However, these two trials can be considered to provide evidence of budesonide efficacy. This is because the likely outcome with no treatment would have been lower than the outcome seen with prednisolone. Although no placebo arm was included in these trials, glucocorticoids are among the most effective drugs to treat the disease in its acute stage by actively suppressing inflammation and inducing clinical improvement or even remission in these CDz patients. In addition, as shown in Table 41 of the MOR, the proportions of budesonide-treated patients attaining significant clinical improvement in studies 3002 and 3013 (52% and 60%, respectively) and those treated with prednisolone in studies 3002 and 3013 (65% and 60%, respectively) were higher than those treated with placebo in studies 3001 and 3025 (20% and 33%, respectively). In other words, according to these comparisons, neither prednisolone nor budesonide appear to be behaving like a placebo in trials 3002 and 3013 although, as already mentioned, one (prednisolone) appears to be more efficacious than the other (budesonide). However, this disadvantage, if real, is overcome by a significant improvement in safety (see below).

In summary, **there are four trials showing ENTOCORT to be effective** in procuring clinical improvement of Crohn's disease. It may have been less effective than prednisolone, but it also appears to be less toxic.

Results of Safety Evaluations

As summarized under Section VII INTEGRATED REVIEW OF SAFETY, A Brief Statement of Conclusions, of the MOR, short-term treatment of patients with active CDz with ENTOCORT 9 mg q.d. for up to 8 to 10 weeks was well-tolerated. The overall incidence of AEs and the AE profile were similar to those seen with placebo treatment, except for those adverse events that are the consequence of corticosteroid treatment. The adverse effects commonly associated with the use of classic corticosteroids in the treatment of CDz (and UC) are:

Sleep disturbance, mood disturbance, moon face, acne, striae, hirsutism, adrenal suppression, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, pseudo-tumor cerebri, infection, edema, impaired wound healing, growth retardation, osteoporosis, aseptic necrosis, etc.

Chronic treatment with classic corticosteroid has been associated in some individuals with suppression of the pituitary-adrenal axis and occasionally has been associated with clinically significant adrenal suppression.

As displayed in Table 44 of the MOR, ENTOCORT was significantly less toxic than prednisolone in disorders of 4 body systems: gastrointestinal, endocrine, psychiatric and skin & appendages. This Table is reproduced below.

Table 44: Summary of the Most Frequently Occurring Body System Disorders in the AE Reporting (≥10%) in Controlled Studies in Active CDz

Disorders by system	Entocort 9mg [n=520]	PL [n=107]	Prednisolone [n=145]	Mesalamine [n=88]	Difference Pred. Vs ENT
Gastro-intestinal	(42)	(44)	(53)	(42)	11%*
Endocrine	(36)	(37)	(48)	(0)	12%*
Body as whole	(30)	(38)	(37)	(24)	7%
Nervous	(28)	(22)	(35)	(19)	7%
Respiratory	(21)	(20)	(20)	(9)	-1%
Psychiatric	(15)	(10)	(26)	(9)	11%**
Skin & appendages	(14)	(16)	(24)	(8)	10%*
Musculo-skeletal	(12)	(9)	(15)	(7)	3%

*= statistically significantly different from Entocort 9mg, p<0.05
 **= statistically significantly different from Entocort 9mg, p<0.01
 p-values were calculated by FDA statistician.

MO Reviewer's Table, summarized from Vol. 36, page 71, modified by the MTL

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Glucocorticosteroid (GCS) side effects

Refer to MOR, Table 45 (reproduced below).

Table 45: the incidences of GCS Side Effects in Clinical Studies in Active CDz

	Entocort total [n=558] (%)	Entocort 9 mg [n=427] (%)	Placebo [n=107] (%)	Prednisolone 40 mg Taper [n=145] (%)
Any GCS side effect	175 (31)	145 (34)	29 (27)	69 (48)**
Moon face	54 (10)	46(11)	4(4)	53 (37)***
Acne	79 (14)	63 (15)	14 (13)	33 (23)*
Bruising easily	70 (13)	63 (15)	12 (11)	13 (9)
Swollen ankles	41 (7)	32 (7)	6 (6)	13 (9)
Hirsutism	22 (4)	22 (5)	2 (2)	5 (3)
Buffalo hump	6 (1)	6 (1)	2 (2)	5 (3)
Skin striae	4 (1)	4 (1)	2 (2)	0
Evaluable patients for following AE*		159	41	
Any of below listed AE		86 (54)	23 (56)	
Insomina		57 (36)	16 (39)	
Mood swings		54 (34)	15 (37)	
Depression		43 (27)	9 (22)	
Hair loss		13 (8)	2 (5)	
<p>*only evaluated in study 08-3025 *= statistically significantly different from Entocort 9 mg, p<0.05 **= statistically significantly different from Entocort 9 mg, p<0.01 ***=statistically significantly different from Entocort 9 mg, p<0.001</p>				
MO reviewer's Table summarized from Vol. 36, page 79, modified by the MTL				

- Among the 7 “more common” AEs that are GCS-related, “moon face” is one of the most relevant. From the ENTOCORT clinical trials experience of 8 weeks treatment, the incidence of “moon face” was smaller with budesonide 9 mg qd (11%) than with prednisolone (37%), 95% CI of the difference: -26% (-34%, -17%). Such incidence appears to be worse than placebo (4%), 95% CI of the difference: 7% (2%, 12%) based on the data pooled from studies 3001, 3025, 3002 and 3013.

- “Acne” appeared to occur more often with prednisolone (23%) than with budesonide 9 mg qd (15%), 95 CI of the difference: 8% (0.4%, 16%). In this regard, budesonide was similar to placebo (13%). 95% CI of the difference: 2% (-6%, 9%).
- As pointed out by the statistician reviewer, the incidences of other GCS-related AEs, “bruise easily”, “swollen ankles”, “skin striae”, “hirsutism”, and “buffalo hump” were similar among budesonide 9 mg qd, prednisolone and placebo.

In summary, a significantly superior safety in terms of higher proportion of patients with normal p-cortisol concentration and a similar or lower incidence of patients with GCS-related AEs was observed in the two prednisolone-controlled trials (3002 and 3013).

Regulatory Recommendations

The MTL agrees with each of the six (6) recommendations for regulatory action formulated by Dr. Ruyi He in his review of NDA 21-324. Since no major issues, for any of the disciplines are pending, the MTL urges the Division Director to finalize all issues related to the labeling and **approve ENTOCORT for the treatment of patients with mild to moderate active CDz involving the ileum and/or ascending colon.**

Because it is less toxic, this novel GCS represents a significant safety improvement over prednisolone.

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader

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**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS MEDICAL OFFICER'S REVIEW**

NDA: 21-324

Sponsor: AstraZeneca LP
725 Chesterbrook Blvd
Wayne, PA 19087-5677

Drug name: **ENTOCORT Capsules** (budesonide modified-release capsules)

Dosage: 9 mg once daily

Route of Administration: Oral

Indication: The treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

Date submitted: January 24, 2001

Date received: January 24, 2001

Date assigned: February 5, 2001

Reviewer: Ruyi He, M.D.

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

The clinical program with ENTOCORT supported that administration of ENTOCORT at a dose of 9 mg once daily is effective in treating mild to moderate Crohn's Disease (CD) involving the ileum and/or ascending colon. One study demonstrated that ENTOCORT 9 mg once daily in the morning was statistically significantly better in inducing remission of CD in comparison with mesalamine ($p=0.001$) with 24% therapeutic gain. Although mesalamine is not approved for CD in the US, it is widely used in this country to treat active CD in clinical practice. In comparison with placebo, Study 08-3001 showed that ENTOCORT 4.5 mg bid was statistically significantly better in inducing remission of CD ($p=0.0004$) with 31% therapeutic gain. Although ENTOCORT 4.5 mg bid in this study was different from the 9 mg qd proposed regimen, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen. An additional placebo-control study (08-3025) showed that ENTOCORT 9 mg once daily in the morning was numerically better in inducing remission of CD with 15% therapeutic gain. The lack of statistically significant difference in this study might be the consequence of less patients enrolled in the placebo group (2:1 enrollment, $n=41$) and more patients with mild disease (71% of CDAI <300 ; median =253) enrolled in comparison with the first placebo study (62% <300 ; median =287). These imbalances might have resulted in a higher placebo response rate (33% in Study 08-3025; 20% in Study 08-3001) and lower dropout rate. Two trials assessed efficacy of ENTOCORT 9 mg once daily in comparison with prednisolone. Identical remission rates (60%) were found in one study and 13% less remission rate (52% vs. 65%) in another. In the latter trial, the difference between the treatment arms was not statistically significant ($p=0.12$). To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD. It is therefore concluded that ENTOCORT at a dose of 9 mg once daily is effective in treating mild to moderate CD involving the ileum and/or ascending colon.

The clinical studies established a favorable safety and tolerability profile for ENTOCORT in the intended population. At therapeutically comparable doses, ENTOCORT 9 mg/day was associated with a significantly lower incidence of glucocorticosteroid (GCS) AEs compared to prednisolone (total GCS side effect $p<0.01$, moon face $p<0.001$ and acne $p<0.05$) and ENTOCORT had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ($p<0.0001$). However, ENTOCORT does have GCS activity because a numerically higher incidence of GCS adverse effects was reported in comparison with placebo.

It is therefore concluded that the therapy with ENTOCORT 9 mg qd has a favorable risk-benefit ratio when considering it as a treatment option for patients with mild to moderate active CD involving the ileum and/or ascending colon. I have the following recommendations for regulatory action:

1. ENTOCORT is approvable as a treatment option for patients with mild to moderate active CD involving the ileum and/or ascending colon from a clinical perspective. The recommended dose of ENTOCORT is 9 mg once daily in the morning for up to 8 weeks. To get ENTOCORT approved, the sponsor has to follow all of the recommendations listed below and do all of the necessary changes in the ENTOCORT labeling.

-
-
3. Submission of pediatric data should be deferred until after approval of NDA 21-324 and pediatric information should not be included in the package insert, because at this time no adequate efficacy and safety data to support use of ENTOCORT in children have been provided.
 4. Partial waiver request for pediatric studies in patients ≤ 5 years of age should be granted, because the number of patients with CD ≤ 5 years of age is very limited.

B. Recommendation on Phase IV Studies

Well control studies should be done in CD patients 6 to 17 years of age to evaluate the safety and efficacy of ENTOCORT in these pediatric populations as a phase IV study commitments.

II SUMMARY OF CLINICAL FINDINGS

A. Brief Overview of Clinical Program

Crohn's disease is an idiopathic, immunologically mediated, inflammatory disease of the gastrointestinal tract. At the present time there is no cure for CD. The goals of medical treatment are to suppress the inflammatory response, permit healing of tissue, and relieve the symptoms of fever, diarrhea, and abdominal pain.

ENTOCORT capsules is a synthetic glucocorticosteroid with mainly local anti-inflammatory properties and with weak mineralcorticoid activity. It is commercially available in the US in several inhalation devices for the local treatment of asthma and allergic rhinitis. ENTOCORT capsules consist of gastro-resistant granules with prolonged release properties. ENTOCORT has extensive first pass metabolism but little systemic availability. The limited bioavailability may result in less glucocorticosteroid (GCS)-related side effects compared to conventional systemically-available steroids.

A total of five completed, controlled, phase IIB/III efficacy and safety trials (Studies 08-3001, 08-3027, 08-3025, 08-3002, 08-3013) in patients with active CD were included in

The five clinical trials are identified as a comparison to mesalamine (08-3027), two placebo-controlled (08-3001 and 08-3025) and two comparisons to prednisolone (08-3013 and 08-3002).

- Study 08-3027 demonstrated that ENTOCORT 9 mg once daily in the morning was significantly better in inducing remission of CD than mesalamine (69% vs. 45%, $p=0.001$) with 24% therapeutic gain. Mesalamine is considered as active comparator because although this drug is not approved for the treatment of CD in the US, it is widely used in this country to treat active CD in clinical practice.
- One of the 2 placebo-control studies (08-3001), showed that ENTOCORT 4.5 mg bid was statistically significantly better in inducing remission of active CD ($p=0.0004$) with 31% therapeutic gain. Although the ENTOCORT 4.5 mg bid regimen is different from 9 mg qd, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety when the dose is given as a once-a-day or two divided dosing regimen. Therefore, study 08-3001 is considered supportive. The other placebo-control study (08-3025) showed that ENTOCORT 9 mg qd was numerically better in inducing remission of CD with 15% therapeutic gain. The lack of statistically significant difference in this study might be the consequence of less patients enrolled in the placebo group (2:1 enrollment, $n=41$) and more patients with mild disease enrolled (median CDAI=253, 71% < 300) compared to the first placebo study (median CDAI=287, 62% < 300). These imbalances might have resulted in a higher placebo response rate (33% in Study 08-3025; 20% in Study 08-3001) and lower dropout rate in Study 08-3025.
- In comparison with prednisolone, equal remission rates (60%) were seen in the ENTOCORT 9 mg qd group and the prednisolone group in Study 08-3013, whereas there was a 13% less remission rate (52%) in the ENTOCORT than in the prednisolone group (65%) in Study 08-3002. In the latter study, however, the difference between the two arms was not statistically significant with $p=0.12$. Owing to inconsistent results, no firm conclusion can be drawn, although ENTOCORT might be less effective than prednisolone. To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD.

C. Summary of Safety

The clinical Phase I-III program for ENTOCORT capsules included a total of 2076 patients and subjects who received at least one dose of study drug or comparators. Of these patients and subjects 1400 received at least one dose of ENTOCORT capsules.

Across the 5 controlled trials in active CD, a total of 993 patients were treated. A total of 651 patients with active CD were treated in the ENTOCORT groups which included 3 different daily doses (3, 9 or 15mg) and 2 different regimens (qd or bid). A total of 107, 146 and 89 patients with active CD were treated with either placebo, prednisolone or mesalamine separately in those 5 clinical studies. The sponsor's clinical development was

sound because it allows comparison of the safety profile of ENTOCORT to a) placebo; b) a widely used glucocorticosteroid (prednisolone) and c) sulfasalazine-like compound (mesalamine).

In those 5 controlled studies in active CD between 58% and 88% of patients were exposed to study drug 8 weeks or more. In the ENTOCORT 9 mg group 84% of the patients were exposed to 8-week treatment or more. The corresponding figures for the placebo and Prednisolone groups were 58% and 88%. Across all treatment groups only 3% or less of the patients received less than one week of treatment.

The median time of exposure was similar in the ENTOCORT 9 mg, placebo and prednisolone groups (68-72 days). In the mesalamine 4 g group the median exposure time was higher (110 days). Thus, based on length of exposure only, more adverse events (AEs) might be expected in the mesalamine group in comparison to the others.

Safety assessments were adequate. There were done at baseline and every follow-up visit.

Short-term treatment of patients with active CD with ENTOCORT capsules 9 mg/day for up to 8-10 weeks was well tolerated. The overall AE incidence and AE profile were similar to those of placebo treatment except for those side effects that are the consequence of corticosteroid treatment. It is therefore concluded that ENTOCORT does have glucocorticosteroid (GCS) effect. Almost half (48%) of the patients on prednisolone reported at least one GCS side effect which was significantly higher than those in the ENTOCORT 9 mg group (34%, $p < 0.01$) or placebo group (27%) respectively. Two specific GCS side effects, acne and moon face, were reported in the prednisolone group 23% and 37% in comparison with 15% and 11% in the ENTOCORT 9 mg group ($p < 0.05$ and $p < 0.001$). Acne and moon face were reported in 13% and 4% of the patients in the placebo group. In comparison with prednisolone, ENTOCORT had statistically significant less AEs in endocrine ($p < 0.05$), gastro-intestinal ($p < 0.05$), skin & appendages ($p < 0.05$) and psychiatric ($p < 0.01$) systems. After 8 weeks treatment, 60-66% of patients in the ENTOCORT group and 26-28% of patients in the prednisolone group had normal cortisol levels (≥ 150 nmol/L) and this indicated that ENTOCORT had statistically significant less suppressing effect on plasma cortisol level and adrenal function at clinical equivalent doses ($p < 0.0001$). There were no trends or patterns of AE that would not be expected with a corticosteroid in the treatment of patients with CD.

No deaths occurred during the course of the trials among the patients in the controlled studies in active CD. The incidence rate of serious adverse events (SAE) was 10% in the ENTOCORT 9 mg group, 13% in the prednisolone 40 mg taper group, 19% in the mesalamine 4 g group and 6% in the placebo group. The majority of the SAEs reported in ENTOCORT-treated patient (50 out of 66) were gastrointestinal symptoms associated with deterioration of the underlying CD requiring hospitalization.

A total of 505 patients were treated and evaluable for AEs in the five controlled long-term (one-year) studies, 208 in the ENTOCORT 6 mg group, 88 in the ENTOCORT 3mg group and 209 in the placebo group. Across these five one-year studies 78% of both the ENTOCORT 6 mg group and the placebo group reported at least one AE. The

corresponding figure in the ENTOCORT 3 mg group was 67%. Of the most commonly reported AE upon one year administration, the symptoms of Cushing Syndrome were reported in 38% of the patients in the ENTOCORT 6 mg group and 24% in the placebo group. Acne was the most frequently reported GCS side effect, with 15% of the ENTOCORT 6 mg patients and 9% of placebo patients. Bruising easily (11%), moon face (11%) and hirsutism (6%) were more common in the ENTOCORT 6 mg group than the placebo group (1%, 6% and 2% respectively). No deaths were reported in the long-term controlled studies. Eight percent (8%) of the ENTOCORT 6 mg patients, 5% of the ENTOCORT 3 mg patients and 10% of the placebo patients were withdrawn due to AEs in the five one-year studies.

In both short-term and long-term studies, the only relevant findings from analysis of laboratory data were some reports of hypokalemia, which probably reflect increased sensitivity to this known effect of glucocorticosteroids.

Due to small numbers of geriatric, pediatric and racial origin other than Caucasian patients no conclusions can be drawn about the safety of ENTOCORT in these populations. The safety of ENTOCORT in pregnancy has not been adequately assessed. Since orally administered budesonide is normally cleared to 85 to 90% by hepatic biotransformation, reducing the dose of ENTOCORT should be considered for those patients with moderate to severe liver disease.

As of 01 June 2000, 182 AE reports, comprised of 383 symptoms from the marketed use of ENTOCORT have been reported to the sponsor which included 23 SAEs and one death. Post-marketing surveillance reports differed slightly in that the most commonly reported AEs were within the skin and appendages disorders with 51 reports, followed by body as a whole with 45 reports. This might be due to the fact that, compared to clinical trials and compassionate use, reports of deterioration of CD demanding withdrawal or hospitalization would normally not be reported.

ENTOCORT is unlikely to inhibit the metabolism of other drugs, including CYP3A4 substrates. CYP3A4 inhibitors will inhibit the metabolism of budesonide resulting in increases in the systemic availability of budesonide. If treatment with ketoconazole, or any other inhibitor of CYP3A4 activity, together with budesonide is indicated, reduction of the budesonide dose should be considered if side effects typical of systemic glucocorticoids occur. Low-dose oral contraceptives do not alter the plasma levels of budesonide. The pharmacokinetics of budesonide was not significantly influenced by concomitant intake of cimetidine or omeprazole.

D. Dosing

The recommended adult dosage for the treatment of mild to moderate active CD involving the ileum and/or the ascending colon is 9 mg taken once daily in the morning for up to 8 weeks. Three different dosing regimens (3, 9 or 15mg/day) were studied for treatment of active CD. After 8 weeks of treatment, the highest remission rate of 51%, was observed in the ENTOCORT 9 mg group, compared with 41% in the 15 mg group and 31% and 20% in the 3 mg and placebo groups, respectively. There was no

statistically significant difference between the ENTOCORT 3 mg and the placebo groups ($p= 0.13$) or the ENTOCORT 9 and 15 mg groups ($p= 0.34$). Therefore, 9 mg/day of ENTOCORT was used in subsequent clinical evaluations and recommended in the label.

E. Special Populations

Across all 5 controlled trials in active CD, a total of 625 (63%, total 991) patients were female. A total of 416 female (64%, total 651) patients with active CD were treated in the ENTOCORT groups which, as already mentioned, included 3 different daily doses (3, 9 or 15 mg) and 2 different regimens (qd and bid). There was no statistically significant difference between males and females for the efficacy analysis. In all treatment groups a higher percentage of female patients (87%) reported AEs, compared to 77% of the male patients. No special pattern of AE was observed based on gender.

The clinical response rates at Week 8 were significantly lower among patients with more severe disease at study entry ($CDAI \geq 300$) than patients who had $CDAI < 300$ ($p < 0.01$).

In the controlled studies in active CD only 30 out of 991 patients (3%) were of a racial origin other than Caucasian. Six patients were black, 3 oriental and 21 were characterized as of 'other' racial origin. Therefore, subgroup analyses of race on response rate and safety did not seem meaningful.

Among the different treatment groups only between 0 and 3.4% of the patients included in the safety analysis of the controlled studies in active CD were 65 years or older. This very small number of patient 65 years and older is inadequate to draw any meaningful conclusions regarding on AE profile in this category of patients.

Also limited was the exposure of ENTOCORT in pediatric patients. The sponsor requests a partial waiver of pediatric studies for patients below 6 years of age with active CD, due to the very small number of patients in this pediatric group. Additionally, the sponsor requests submission of pediatric data deferred until after approval of this NDA, as the pediatric development program is still ongoing.

The safety and efficacy of ENTOCORT in pregnancy has not been evaluated. Animal studies indicate an increased risk for injury to the fetus (cleft palate, skeletal malformation) when the mother is treated with glucocorticoids. However, the relevance of this pre-clinical finding to man is unclear.

ENTOCORT was extensively metabolized in the liver (85-90%) and was likely to be influenced by changes in the liver function. Plasma cortisol was suppressed approximately twice as much in the cirrhotic patients as in the healthy subjects. Consequently, patients with moderate to severe liver disease should be monitored for hypercorticism and reducing the dose of ENTOCORT should be considered in these patients.

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

The sponsor proposed that ENTOCORT Capsules (budesonide extended-release capsules) is used for the indication of the treatment of mild to moderate active CD involving the ileum and/or the ascending colon. The recommended adult dosage is 9 mg taken once daily orally in the morning for up to 8 weeks. ENTOCORT capsules should be swallowed whole and not chewed or broken. Treatment with ENTOCORT capsules can be tapered to 6 mg daily for 2 weeks prior to complete cessation.

The sponsor proposed that for children weighing 30 kg or more, the recommended starting dose of ENTOCORT is 9 mg taken once daily. Reducing the dose should be considered if signs and/or symptoms of hypercorticism develop. However, the sponsor did not submit any efficacy data of ENTOCORT in pediatric patients. The sponsor requests that submission of pediatric data be deferred until after approval of NDA 21-324, as the pediatric development program is still ongoing.

Crohn's disease is an idiopathic, immunologically mediated, inflammatory disease of the gastrointestinal tract. It predominates in the lower part of the small intestine (ileum) and in the large intestine (right colon), with approximately 70% of patients with CD exhibiting small intestinal or ileocolonic involvement. Although CD is usually not fatal, it may progress to serious, life-threatening gastrointestinal complications such as obstruction, perforation, abscess, peritonitis, and hemorrhage. CD can also cause ulcers that tunnel through the affected area into surrounding tissue such as the bladder, vagina, or skin. As many as 70% of patients with CD require surgery during their lifetime to treat infected fistulas, with many requiring surgery more than once. Extraintestinal and systemic complications of CD include arthralgia, malnutrition, skin problems, kidney stones and gallstones, and inflammation of the eyes or mouth.

A diagnosis of CD often means life-long medical care, potential surgery, substantial impact on day-to-day functioning, and considerably reduced quality of life. At the present time there is no cure for CD. The goals of medical treatment are to suppress the inflammatory response, permit healing of tissue, and relieve the symptoms of fever, diarrhea, and abdominal pain.

To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD. Prednisolone syrup has been approved in the U.S. for the indication of tiding the patient over a critical period of the disease in CD. The benefits of these drugs in CD, however, are offset by safety concerns associated with their use. The systemic action of orally administered glucocorticosteroids affects every organ system, and long-term use of these drugs results in suppression of endogenous adrenal function. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor, is the only non-glucocorticosteroid therapy approved in the United States for the treatment of CD, and is indicated for use in patients with moderate to severe CD who have had an inadequate response to conventional

therapy. Infliximab must be administered intravenously, and safety in active CD has not been established for more than one dose. A single infusion of infliximab decreases symptoms in about two-thirds of patients and induces remission in about one-third within four weeks. Other drugs used to treat active CD, but not approved for this indication in the United States, include broad-spectrum antibiotics, immunosuppressives, such as azathioprine and 6-mercaptopurine and 5-aminosalicylic acid (i.e., sulfasalazine and mesalamine).

Budesonide is a synthetic glucocorticosteroid with pronounced local anti-inflammatory properties and weak mineralcorticoid activity. It is commercially available in several inhalation devices for the local treatment of asthma and allergic rhinitis. The anti-inflammatory activity of budesonide is high, and the glucocorticosteroid receptor affinity is about 15 times that of prednisolone and about 200 times that of hydrocortisone according to the sponsor. Budesonide offers potential advantages over conventional systemically-available steroids which stem from its high intrinsic glucocorticosteroid activity and rapid and extensive first-pass inactivation in the liver. Budesonide was developed in the gastric resistant formulation, ENTOCORT capsules, specifically to exploit its favorable pharmacokinetic properties for the treatment of CD. ENTOCORT capsules consist of gelatin capsules containing gastro-resistant granules with prolonged release properties. A coating ——— protects the granules from gastric juice but dissolves at a pH above 5.5, normally when the pellets enter the duodenum. After budesonide is readily taken up by the intestinal mucosa, it is transported to the liver where it undergoes extensive first pass metabolism to metabolites of low or negligible glucocorticoid activity. This extensive first pass metabolism for budesonide ensures little systemic availability, which may result in less glucocorticosteroid (GCS)-related side effects compared to conventional systemically-available steroids.

The original ——— for ENTOCORT was submitted on December 14, 1994 for the treatment of mild to moderate active CD involving the ileum and/or ascending colon. Since Phase I and II studies had been conducted earlier in Europe and Canada, the End-of-Phase II Meeting took place on May 18, 1995 shortly after the IND was submitted. During that meeting the clinical development program was discussed which included the summarized results of Studies 08-3001, 08-3002 and 08-3013. The Study 08-3027 was ongoing at that time. The study plan protocol 08-3025 was mainly discussed at that meeting. Protocol 08-3025 was a placebo-controlled study entitled "budesonide controlled ileal release capsules (9 mg) once and (4.5 mg) twice daily in active Crohn's disease". The Division suggested that the firm consider adding an active control, such as another steroid. In addition, since Protocol 3013 indicates that 4.5 mg budesonide BID is inferior to 9 mg QD, the Division suggested that the firm consider replacing the 4.5 mg BID arm with a higher QD dose, such as 12 mg. However, the sponsor did not evaluate this dose regimen. The content and format of this NDA were discussed at a pre-NDA meeting held on May 25, 2000. No Advisory Committee Meeting was held for this application.

ENTOCORT 3 mg capsules were first approved for prescription use in March 1995 in Sweden. As of 1 June 2000, approval has been granted in 42 countries outside of the

United States,

The primary indication is for the induction of remission of active CD localized to the ileum and ascending colon. The indication of maintenance of remission has been approved in 24 countries.

Up to March 30, 2001, Entocort for acute treatment has not been withdrawn or rejected in any country. The marketing application for the prolongation of remission/maintenance of remission was rejected in However, the sponsor did not apply for this particular indication in this submission.

Budesonide is commercially available in the United States in several inhalation devices for the local treatment of asthma and allergic rhinitis. The following NDAs with budesonide have been submitted in the United States:

- Rhinocort pMDI 50 µg/dose, NDA 20-233, approved 1994.
- Pulmicort Turbuhaler 200 and 400 µg/dose, NDA 20-441, approved 1997.
- Rhinocort Aqua nasal spray, suspension. 32 and 64 µg/dose, NDA 20-746, approved 1999.
- Pulmicort Nebulizer suspension, 0.125, 0.25 and 0.5 mg/mL, NDA 20-929, approved 2000.

ENTOCORT capsules is budesonide modified-release capsules and has not been approved in the United States for any indication.

II. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY AND BIOPHARMACEUTICS REVIEWS

The chemistry, toxicology and biopharmaceutics studies are presented and discussed in detail in the FDA Chemist, Pharmacology and Pharmaceutics reviews respectively. Below I have summarized some of the major clinically relevant findings reported by the sponsor.

A CHEMISTRY

ENTOCORT capsules are formulated as a modified release system that can be described as a multi-unit preparation of coated granules with both delayed and extended release properties. The market formulation is a capsule dosage form containing a dose of 3 mg budesonide granules encapsulated in a hard gelatin capsule. The product strength is determined by encapsulating a specific amount of granules, based on the actual amount of budesonide in the granules. In the clinical program, the strengths 1.5, 2.25 and 3 mg have been used, however, the composition of the granules is common for all strengths.

Entocort 3 mg (budesonide modified-release capsules) is the product name. The product is also referred to as ENTOCORT Capsules 3 mg or Budesonide CIR capsules 3 mg in the application.

Briefly, the manufacture of ENTOCORT capsules is comprised of the following sequential steps: _____

Entocort capsules are sensitive to moisture. therefore the capsules are packaged in _____

Thirty-six months of data from long term storage conditions at 30°C/75% RH and six months of accelerated storage conditions at 40°C/75% RH are available on _____ batches of the drug product. They are packaged in _____ tamper-evident _____ in the cap for 100 capsules. The sponsor proposed _____ months expiration date.

B. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Pharmacology

Budesonide has a very high affinity for the glucocorticoid receptors, an extensive first-pass metabolism and a favorable combination of water solubility and moderate lipophilicity, this compound exhibits suitable properties for topical anti-inflammatory treatment of the intestinal wall.

The effects of budesonide on the production of Th1- and Th2-type cytokines were studied *in vitro*. A dose-dependent inhibition of the production of both INF- γ and IL-4 was observed. Prevention of immune-mediated epithelial dysfunction was demonstrated to be due to inhibition of immunocyte activation (T cells and/or monocytes) and not to direct epithelial action. Budesonide also inhibits release of pro-inflammatory cytokines (IL-1 β , IL-6 and IL-8) by mononuclear cells of the intestinal lamina propria as well as peripheral monocytes in a dose-dependent manner. Stimulation of intestinal epithelial cells resulted in inhibition of DNA binding activity and nuclear expression of NF-kB.

Uptake and retention of locally administered ³H-budesonide and ³H-prednisolone-21-disodium phosphate was studied *in vivo* in the luminally perfused rat ileum. Both compounds were rapidly taken up into the ileal tissue. Both compounds were found in high concentration in the mucosa and submucosa. When related to the perfused concentration, budesonide was, however, taken up from the intestinal lumen to a greater extent than prednisolone (15-fold greater at 20 min postdosing). In addition, budesonide was better retained in the intestinal tissue (50-fold greater at 4 hours postdosing). The high uptake of budesonide was not reduced by a mucosal exudation induced by allergen challenge.

Budesonide was at least 30 times more potent than prednisolone in reducing ileal

inflammation and induced relatively fewer systemic side effects than prednisolone. In this rat model of IgE-mediated ileal plasma exudation, the effects of a single topical administration of budesonide were evaluated. Significant local anti-inflammatory effects were observed in the gut mucosa a few hours postdosing without systemic effects. The effects of budesonide on plasma exudation, hyperemia and epithelial permeability were also studied after intrarectal administration to rats with oxazolone-induced colitis. Topical treatment with budesonide induced a marked inhibition of the vascular leakage but had no significant effect on the diminished epithelial barrier function.

The effects of local or parenteral administration of budesonide were also assessed in the acetic acid-induced colitis model in rats. It was demonstrated that budesonide could effectively prevent colitis induced by acetic acid in rats in a dose-dependent manner with minimal side effects.

A study comparing the effects of plain and controlled-ileal release (CIR) formulations of budesonide on intestinal inflammation was conducted in hamsters. Intestinal inflammation was induced by administration of trinitrobenzene sulphonic acid (TNBS). CIR budesonide was significantly more effective in reducing inflammation than plain budesonide. These results suggested that the site of delivery influences the effectiveness of budesonide and that local (topical) rather than systemic action is primarily responsible for its anti-inflammatory effect.

Toxicology

After oral administration of budesonide to mice and rats, the estimated values for LD50 were more than 800 and 400 mg/kg, respectively.

In mice, a 3-month oral (drinking water) toxicity study was performed as a dose range-finding study for the subsequent carcinogenicity study. Budesonide was given at dosage levels ranging from 10 to 700 µg/kg/day. A reduction in body weight gain was observed at the dose of 700 µg/kg (1600 µmol/kg).

In rats, budesonide was administered orally (gavage) at dosage levels ranging from 0.05 to 50 mg/kg/day for one month. Effects typical of glucocorticoid treatment were noted at 0.05 mg/kg/day (thymic atrophy) and at 0.5 mg/kg/day and 5 mg/kg/day (decrease in white blood cell counts, atrophy of lymphoid organs and adrenal glands). In addition, at 5 mg/kg/day, gastric ulcerations and intestinal bleeding were observed as well as pronounced systemic toxicity.

In dogs, an 1-month oral toxicity study was conducted with budesonide at dosage levels ranging from 0.01 to 1.0 mg/kg. The main treatment-related findings included decrease of plasma cortisol, increase of alkaline phosphatase and alanine aminotransferase activities, atrophy of adrenals and lymphoid organs and slight enlargement of the liver. There were no adverse effects on the gastrointestinal tract at any dose level.

In the 4-week repeated dose toxicity study, budesonide CIR was administered orally at

dosage levels ranging from 100 to 10,000 $\mu\text{g}/\text{kg}/\text{day}$. There were no treatment-related clinical signs or mortality. There were no treatment-related effects on body weight, food consumption, hematologic and serum biochemistry parameters, organ weight, macro- or microscopic examinations. The plasma concentrations obtained were low and the pooled peak of plasma concentration (C_{max}) reached at 3 hours postdosing ranged between 0.18-0.23 nmol/l, 0.71-0.91 nmol/l and 1.36-2.34 nmol/l in the low-, mid- and high-dose groups, respectively.

In the 26-week repeated dose toxicity study, budesonide CIR was administered orally at dosage levels ranging from 0.5 to 5.0 $\text{mg}/\text{kg}/\text{day}$. There were no treatment-related clinical signs or mortality. A treatment-related decrease in body weight gain/body weight loss was noted in the 2.0 and 5.0 $\text{mg}/\text{kg}/\text{day}$ groups. There were no treatment-related changes in food consumption, hematology or ophthalmic examination. Treatment-related changes in serum biochemistry were limited to a slight decrease in cortisol levels, mainly in the 2.0 and 5.0 $\text{mg}/\text{kg}/\text{day}$ groups. An increase in plasma protein (and globulin) in males at 5.0 $\text{mg}/\text{kg}/\text{day}$ and an increase in glucose in females at 5.0 $\text{mg}/\text{kg}/\text{day}$ were also noted. At necropsy, an increase in mean liver weight and a decrease in mean adrenal weight were noted in the 5.0 $\text{mg}/\text{kg}/\text{day}$ group. There were no treatment-related macroscopic findings. At histopathological examination, a decrease in thymus cellularity was seen in 2 males in the 5.0 $\text{mg}/\text{kg}/\text{day}$ group and a dose-related increased incidence of reduced adrenal cortical width was observed. Concentrations of budesonide were determined 3 hours postdosing in pooled plasma samples. A dose-related increase in plasma concentration was noted. Plasma concentrations over the study period

Carcinogenicity

In the CD-1 mouse carcinogenicity study, budesonide was given orally (drinking water) for 91 weeks at dosage levels of 10, 50 or 200 $\mu\text{g}/\text{kg}$. At the end of the study, there was no evidence of carcinogenic effects.

In the Sprague-Dawley rat carcinogenicity study, budesonide was given orally (drinking water) for 104 weeks at dosage levels of 10, 25 or 50 $\mu\text{g}/\text{kg}$. At the end of the study, at histopathologic examination, a significant increase in the incidence of primary hepatocellular neoplasms (neoplastic nodules and hepatocellular carcinomas) was noted in the 25 and 50 $\mu\text{g}/\text{kg}$ groups. In addition, a significant increase in the number of astrocytomas in the 50 $\mu\text{g}/\text{kg}$ -treated males was observed. A primary glial tumor (oligodendroglioma) was also seen in one 25 $\mu\text{g}/\text{kg}$ -treated male.

In a second carcinogenicity study done in male Sprague-Dawley rats, budesonide was administered orally (drinking water) at a dose of 50 $\mu\text{g}/\text{kg}$. In this study, prednisolone and triamcinolone acetonide were used as reference compounds and were administered orally (drinking water) at a dose of 400 and 15 $\mu\text{g}/\text{kg}$, respectively. Two additional groups were given drinking water and used as control groups. There was no evidence of treatment-related effects in the brain. The incidence of combined hepatocellular

adenomas and carcinomas was statistically significantly increased in all treated groups compared to the combined controls. There were no statistically significant differences in tumor incidence among the treated groups.

Genetic Toxicology Studies

A series of *in vitro* and *in vivo* studies were performed to evaluate the potential genotoxic effects of budesonide. These assays included five *in vitro* studies: two Ames tests, mouse lymphoma mutagenicity test, DNA repair analyses in rat hepatocytes and structural chromosome aberrations in human lymphocytes, and two *in vivo* assays: mouse micronucleus test and sex-linked recessive lethal test in *Drosophila melanogaster*. There were no indications of genotoxicity in any of these assays.

C. MICROBIOLOGY

No microbiology information is included in this application.

D. PHARMACOKINETICS

Oral bioavailability was relatively high in the mouse (35%) and rat (22-32%); but somewhat lower in dog (9-19%). In rat, the absorption rate was slower after oral administration than after inhalation with a maximum concentration at 0.5 hour postdosing. Oral bioavailability was also determined in Cynomolgus monkeys after administration of budesonide controlled ileal release (CIR) at dose levels of 1.0 and 10 mg/kg. The time for peak plasma concentration (T_{max}) was 3.0 hours, the mean absorption time (MAT) was 4.8 and 5.7 hours and the systemic bioavailability versus intravenous administration was 0.9 and 1.4% after 1 and 10 mg/kg, respectively.

Budesonide is oxidatively biotransformed by cytochrome P450 3A enzymes in human liver microsomes. The major two metabolites are 16-hydroxyprednisolone and 6-hydroxybudesonide. The metabolites have a much lower glucocorticoid receptor potency than budesonide and their topical anti-inflammatory potency appears to be even lower.

Excreted metabolites are predominantly found in feces (biliary excretion) after dosing by various routes in rats and dogs. In rats, after oral administration of ³H-budesonide, approximately 10% of the radioactivity is recovered in the urine and approximately 80% in the feces. In urine and bile samples, only budesonide's metabolites were found, indicating an extensive biotransformation of the compound. Whether these metabolites undergo EPHB cycling is not known.

III. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The human pharmacokinetics and pharmacodynamics studies are presented and discussed in detail in the FDA Biopharmaceutics review. Below I have summarized the major clinically relevant findings reported by the sponsor.

A. Absorption

Between 43 and 69% (range of means in individual studies) of an oral ENTOCORT dose was absorbed at ileum and ascending colon. The modified-release [controlled ileal release (CIR)] formulation slightly delays absorption and prolongs rate of elimination without affecting total extent of uptake - by this the delivery of budesonide in ileum and ascending colon is improved relative to a plain formulation. A low systemic availability of 9-20% demonstrates an extensive first-pass elimination. Food and gastric emptying time has no significant impact on the absorption of budesonide from ENTOCORT at the target region. The pharmacokinetics is dose-proportional between 3 and 15 mg.

B. Distribution and Elimination

A high volume of distribution (≥ 2 L/kg) in combination with a high plasma protein binding (85-90%) indicates a high tissue affinity of budesonide. Budesonide is biotransformed into its 2 major metabolites, 6 β -hydroxy-budesonide and 16 α -hydroxy-prednisolone by CYP3A4. After oral and intravenous doses of ³H-budesonide, 60% and 63% of the recovered radioactivity was found in urine, respectively, with the rest being found in feces.

C. Disposition in Subpopulations

Systemic availability was on average 2.5-fold higher in cirrhotics compared with healthy controls. Moderate liver impairment demonstrated a more pronounced difference than mild liver impairment. Reducing the dose of ENTOCORT should be considered if signs and/or symptoms of hypercorticism develop in patients with moderate to severe liver disease. In renally impaired patients and in the elderly, no major changes in the pharmacokinetics of budesonide are expected. An interim evaluation of an ongoing study in children aged 9-13 suggests that budesonide exposure and systemic effects are similar as in adults following 9 mg of ENTOCORT. While absorption parameters appear similar in children and adults, systemic availability is reduced (by 45% in the interim evaluation). The pharmacokinetics of budesonide are not affected by gender.

D. Drug Interactions

Budesonide is unlikely to inhibit the metabolism of other drugs, including CYP3A4 substrates, mainly due to the very low plasma concentrations obtained with the compound. Budesonide does not have any effect on the plasma levels of oral contraceptives containing the CYP3A4 substrate ethinyl estradiol. Strong CYP3A4 inhibitors, such as ketoconazole, will inhibit the metabolism of budesonide resulting in