CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	203-634
Supporting document/s:	0001
Applicant's letter date:	December 16, 2011
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Product:	UCERIS (Budesonide MMX)
Indication:	For the treatment of mild to moderate ulcerative colitis (UC).
Applicant:	Santarus, Inc.
Review Division:	Division of Gastroenterology product (HFD-180)
Reviewer:	Dinesh Gautam, Ph.D.
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Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, approval of the NDA application is recommended.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of UCERIS generally conforms to the format specified under 21CFR 201.57(c)(14) Requirements for PLR (Physician's Labeling Rule) Prescription Drug Labeling. However, the following changes should be incorporated.

8.1 Pregnancy

Sponsor's version:

Teratogenic Effects

Pregnancy Category C

(b) (4) 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.

Evaluation: No changes are recommended in this section.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Evaluation: No changes are recommended in this section.

(b) (4)

Sponsor's version:

(b) (4)

(b) (4)

Sponsor's version:

(b) (4)

Evaluation: Section (b) (4) is not required and should be deleted.

1.2 Brief Discussion of Nonclinical Findings

For nonclinical safety, the applicant relied on the Agency's previous assessment of safety of budesonide. In addition, as per the Agency's recommendation, a 28-day repeated dose oral toxicity study in Cynomolgus monkeys was conducted and the study report was submitted in this NDA application.

This NDA is submitted under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. Specifically, this NDA is supported by reference to the Agency's previous findings of safety and available information on the toxicology of budesonide. In addition, the applicant provided published literature on the pharmacology and pharmacokinetics of budesonide.

The repeated dose toxicology study of budesonide in cynomolgus monkeys showed that budesonide was well tolerated in this species. No treatment-related toxicological adverse effects were observed in animals receiving the drug.

Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the

Drosophila melanogaster sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test.

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 µg/kg. In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 µg/kg and above. No tumorigenicity was seen in female rats at oral doses up to 50 µg/kg. In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 µg/kg. However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 µg/kg. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 µg/kg.

Budesonide had no effect on fertility in rats at subcutaneous doses up to 80 µg/kg. 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 a subcutaneous dose of 20 µg/kg. No such effects were noted at 5 µg/kg.

Pharmacologic Activity:

Budesonide is a glucocorticoid with high topical anti-inflammatory activity with reduced adverse systemic activity. Budesonide exhibits potent anti-inflammatory effects in the treatment of bronchial asthma when administered via the pulmonary route. Budesonide has also been shown to exhibit significant anti-inflammatory activity in the lower GI tract in the treatment of Crohn's disease and ulcerative colitis. Budesonide (Entocort® EC) is currently approved for the treatment of CD.

Budesonide has strong glucocorticoid receptor affinity and an effective first pass metabolism by the liver with a short half-life. These attributes permit budesonide to act rapidly and locally in the gut mucosa for treatment of inflammatory disorders such as CD and UC. Once absorbed into the systemic circulation, budesonide is rapidly metabolized in the liver and inactivated.

2 Drug Information

2.1 **Drug:** UCERIS (Budesonide MMX) Tablets

2.1.1 CAS Registry Number (Optional)

51333-22-3

2.1.2 Generic Name

Budesonide

2.1.3 Code Name

CB-01-02

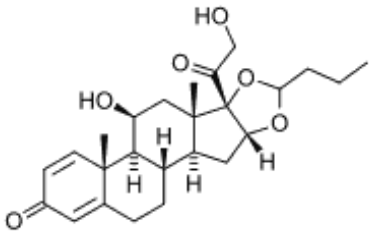
2.1.4 Chemical Name

16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione.

2.1.5 Molecular Formula/Molecular Weight

$C_{25}H_{34}O_6$ / 430.5

2.1.6 Structure



2.1.7 Pharmacologic class

Glucocorticoid.

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA: 21-324: Entecort®, AstraZeneca, LP, DE.

2.3 Clinical Formulation

2.3.1 Drug Formulation

The Budesonide MMX® extended release tablets contain 9 mg of Budesonide USP, along with other excipients (see Table below). Budesonide MMX Tablets are white to off white, round, biconvex, film-coated tablets with debossed “MX9” on one side of the tablet. The composition of the drug product is shown in the applicant’s Table below.

Table 1. Budesonide MMX™ Extended Release Tablets, 9 mg, Composition

Components	Amount (mg)	Function	Reference to Standards
		(b) (4)	
Budesonide	9.0	Active Ingredient	USP
Stearic Acid	(b) (4)	(b) (4)	NF
Lecithin			NF
Microcrystalline cellulose			NF
Hydroxypropylcellulose			NF
Lactose (b) (4)			NF
Silicon Dioxide			NF
Magnesium Stearate			NF
(b) (4)			NF
		(b) (4)	
Methacrylic Acid Copolymer, Type A		(b) (4)	NF
Methacrylic Acid Copolymer, type B			NF
Talc			NF
Titanium Dioxide			NF
Triethylcitrate			NF
(b) (4)			NF
Tablet Weight:			

* (b) (4)

2.3.2 Comments on Novel Excipients

No novel excipients were used in the formulation of the drug product.

2.3.3 Comments on Impurities/Degradants of Concern

The known impurities that are tested as part of the budesonide drug substance analysis can be classified into three categories: Related compounds, inorganic impurities, and residual solvents. The known process related impurities and degradation products are presented in the Table below.

Table 1. Related Compounds

Name	Source	Limit
(b) (4)		

Inorganic impurities are controlled and are not more than (b) (4) as per the USP <281> Residue on Ignition test. Similarly, (b) (4) that could be potentially present in the final product are (b) (4). Each (b) (4) is routinely evaluated by a validated GC method. The acceptable limits for (b) (4) are NMT; (b) (4) ppm ((b) (4)) and NMT (b) (4) ppm ((b) (4)). Thus, based on ICH Q3B(R2) guidance, these impurities are within the acceptable limits.

2.4 Proposed Clinical Population and Dosing Regimen

UCERIS (budesonide) Tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. The proposed dosing regimen is one tablet daily for up to 8 weeks.

2.5 Regulatory Background

A Type B pre-IND meeting was held on June 8, 2006, and the Agency asked the applicant to conduct a 4-week repeated-dose oral toxicology study with budesonide tablets in monkeys. The applicant has submitted the final report of the 4-week oral toxicology study in monkeys in this NDA application.

3 Studies Submitted

The final report of the 28-day monkey toxicology study was submitted. In addition, published pharmacology, pharmacokinetic and toxicology studies with budesonide were submitted.

3.1 Studies Reviewed

Relevant published pharmacology, pharmacokinetic, and toxicology studies submitted are reviewed. In addition, the 4-week toxicology study in monkeys is reviewed.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None.

4 Pharmacology

The applicant submitted available published pharmacology studies of budesonide, and relevant studies are reviewed in the following sections:

Inhibitory effects of budesonide, desloratadine and dexamethasone on cytokine release from human mast cell line (HMC-1) Y. Zhao, P. C. Leung, K. S. Woo, G. G. Chen, Y. O. Won, S. X. Li and C. A. van Hasselt. Inflamm. res., 53 (2004); 664–669

Human leukemic mast cell line (HMC-1) produced substantial amounts of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-8 and smaller amounts of TNF-α, IL-4 and IL-6 after being stimulated with phorbol 12- myristate 13-acetate (PMA) together with ionomycin (A23187). Cells were pre-incubated with budesonide, desloratadine and dexamethasone for 1 h prior to stimulation with PMA + A23187 for 6, 12 and 24 h. Budesonide and dexamethasone had potent inhibitory effects and desloratadine had modest inhibitory effects on the release of these cytokines. Budesonide was more potent than dexamethasone at most concentrations and time points. IL-4 was the cytokine which was most susceptible to inhibition by the three tested drugs. The inhibitory effects, in some cases, were time- and concentration-dependent. The study showed that budesonide had a potent inhibitory effect on cytokine release from HMC-1. Its potency was greater than that of both dexamethasone and desloratadine.

Differential glucocorticoid effects on repair mechanisms and NF-κB activity in the intestinal epithelium. (MN Goke et al, Regulatory Peptides, 105 (2002); 203– 214).

Glucocorticoids are effective agents in the management of inflammatory bowel diseases including UC. In vitro effects of budesonide and prednisolone on proliferation, restitution, and apoptosis as well as their effects on activity and expression of nuclear factor (NF)- κB, a known regulator of apoptosis and inflammation, in intestinal epithelial cells were evaluated. Non-transformed rat jejunum epithelial cells (IEC-6) were cultured in the presence and absence of various concentrations of prednisolone and budesonide. IEC-6 cell proliferation was assessed by [^{3}H]-thymidine incorporation. Restitution was analyzed by an IEC-6 in vitro assay. Apoptosis was evaluated by ELISA and fluorescence microscopy. DNA binding activity and nuclear expression of NF-κB was determined by electrophoresis mobility shift assays and Western blotting, respectively. Prednisolone and budesonide stimulated IEC-6 cell proliferation at low to medium concentrations (prednisolone: 10^{-9} to 10^{-6} M; budesonide: 10^{-11} to 10^{-8} M). In contrast, high concentrations (> 5 x10^{-5} M) had inhibitory effects on proliferation. 10^{-7} M prednisolone and 10^{-8} M budesonide increased restitution of IEC-6 cells, whereas high concentrations (10^{-4} M) of prednisolone and budesonide decreased restitution. Apoptosis of IEC-6 cells were substantially enhanced by 10^{-4} M budesonide; apoptosis was slightly increased by the highest prednisolone concentration (5 x10^{-4} M). Furthermore, both glucocorticoids inhibited DNA binding activity and nuclear NF-κB expression in IEC-6 cells in a dose- and time-dependent fashion. This study suggests that budesonide may elicit its anti-inflammatory effects by modulation of the transcription factor NF-κB.

Anti-inflammatory effects of budesonide in intestinal epithelial cells. (MF Fredin et al, Pharmacological Research, 52 (2005); 422–428).

In this study the anti-inflammatory effects of budesonide was investigated on Caco-2 cells when co-cultured with LPS-stimulated macrophages or with conditioned medium. The mRNA expression of the chemokines IL-8 and ENA-78 were upregulated in Caco-2 cells, being more pronounced in the co-culture than the conditioned medium. The induction of ENA-78 was higher than IL-8. Budesonide decreased both IL-8 and ENA-78 mRNA levels in a dose-dependent manner. A reduction in transepithelial electrical resistance (TEER) and an increase in the apical-basolateral transport of fluoresceinated sulfonic acid (FS) were observed in the Caco-2 cells both in co-cultures and in conditioned medium. Budesonide counteracted the reduction in TEER but had no effect on fluoresceinated sulfonic acid (FS) transport. The reduction in TEER by budesonide was considered to be related to the anti-inflammatory effects on intestinal epithelium cells.

Glucocorticoid availability in Colonic Inflammation of Rat (P. Ergang et al, Dig Dis Sci, (2008); 53: 2160–2167).

It is known that there is involvement of pro-inflammatory cytokines in the regulation of the local metabolism of glucocorticoids via 11b-hydroxysteroid dehydrogenase type 1 and type 2 (11HSD1 and 11HSD2). Changes in the local metabolism of glucocorticoids during colonic inflammation induced by trinitrobenzene sulfonic acid (TNBS) in rats and the consequences of corticosterone metabolism inhibition by carbenoxolone on 11HSD1, 11HSD2, cyclooxygenase 2 (COX-2), mucin 2 (MUC-2), tumor necrosis factor alpha (TNF-α), and interleukin 1beta (IL-1β) were examined. The metabolism of glucocorticoids was measured in tissue slices in vitro and their 11HSD1, 11HSD2, COX-2, MUC-2, TNF- α, and IL-1β mRNA by quantitative reverse transcription-polymerase chain reaction (rtPCR). Colitis produced an up-regulation of colonic 11HSD1 and down-regulation of 11HSD2 in a dose-dependent manner, and these changes resulted in a decreased capacity of the inflamed tissue to inactivate tissue corticosterone. Similarly, 11HSD1 transcript was increased in colonic intraepithelial lymphocytes of TNBS-treated rats. Topical intracolonic application of carbenoxolone stimulated 11HSD1 mRNA and partially inhibited 11HSD2 mRNA and tissue corticosterone inactivation and these changes were blocked by mifepristone. The administration of budesonide mimicked the effect of carbenoxolone. In contrast to the local metabolism of glucocorticoids, carbenoxolone neither potentiated nor diminished gene expression for COX-2, TNF-α, and IL-1β, despite the fact that budesonide down-regulated all of them. These data indicate that inflammation is associated with the down-regulation of tissue glucocorticoid catabolism. However, these changes in the local metabolism of glucocorticoids do not modulate the expression of COX-2, TNF-α, and IL-1β in inflamed tissue.

Effects of Plain and Controlled-Ileal-Release Budesonide Formulations in Experimental Ileitis (Boyd AJ. et al, Scand J Gastroenterol1995; 30: 974-81).

The effects of plain and controlled-ileal-release (CIR) budesonide on trinitrobenzene sulfonic acid (TNBS)-induced intestinal inflammation in hamsters were examined after oral administration of the drug. The doses used were 200 and 800 µg/kg/day (plain budesonide), or 200 µg/kg/day (CIR budesonide). The pre-treatment groups received the drug or placebo 2 days before the induction of inflammation and the post-treatment

groups received the drug from Day 7 after the induction of inflammation. The animals were killed after 2 weeks and inflammation was assessed by histologic examination of the intestine and by measuring mastocytosis and myeloperoxidase activity.

Two weeks after TNBS treatment, ileal segments showed clear histologic evidence of inflammation and increased levels of tissue myeloperoxidase activity (control segments, 0.300±0.001 units/g; TNBS-treated segments, 9 units/g). Treatment with 200 µg /kg/day of plain budesonide had no effect on the intestinal inflammation as assessed by histological examination; the 800 µg/kg/day dose caused a decrease in the histologic appearance of inflammation in both pre- and post- treatment groups. This dose also caused a significant decrease in the mast cell numbers (43% and 27% decreases in pre- and post-treatment groups respectively) as compared with controls. Treatment with the CIR formulation also caused an improvement of the histologic appearance of inflammation, decreased the number of mast cells (31.7% and 36% in pre- and post-treatment groups respectively). Treatment with both formulations of budesonide (800 µg /kg/day plain and 200 µg/kg/day CIR) caused decreases in the myeloperoxidase activities of the inflamed intestines. Treatment with 800 µg/kg/day of plain budesonide caused 87.7% and 62.2% decreases in the myeloperoxidase levels in the pre- and post-treated animals respectively; the 200 µg /kg/day dose of the CIR formulation caused 77.8% and 67.8% decreases of the enzyme activity respectively. Thus, oral CIR budesonide was effective in reducing trinitrobenzene sulfonic acid induced inflammation in experimental animals.

Oxazolone-induced Colitis in Rats: Effects of Budesonide, Cyclosporin A and 5-Aminosalicylic Acid (Ekstrom, GM, Scand J. Gastroenterol1998; 33: 174-179).

The effects of budesonide and other anti-inflammatory agents were examined in oxazolone-induced colitis in rats. Dark Agouti rats were skin-sensitized with oxazolone and further challenged with intra-rectal oxazolone. The animals were treated with the drugs twice: the day before and the day after the challenge. The following drugs were used: budesonide (430 µg/kg intra-rectally), 5-ASA (21.5 mg/kg intrarectally), cyclosporin-A (15 mg/kg orally) and prednisolone (20 µmol/kg i.p.). In the sensitized rats challenged with intra-rectal oxazolone, there were marked inflammation of the distal colon (inflammation score, 2.3±0.4 vs. 0.6±0.3 in unchallenged rats) that was associated with increased colon weights (51%) and myeloperoxidase (700%) activity. Treatment with budesonide, cyclosporin or prednisolone caused significant reductions of the colonic weights and myeloperoxidase activities, while 5-ASA had no effect. Budesonide treatment caused about 21% and 47% reductions of the, colonic weight and myeloperoxidase activities respectively.

Plasma Exudation, Hyperemia, and Epithelial Permeability in Rats with Oxazolone-Induced Colitis: Modulatory Effects of Budesonide (Ekstrom GM and Anderson SE, Scand J Gastroenterol 2000; 35: 190-197).

The effects of budesonide on the inflammatory changes in oxazolone-induced colitis in the rat colon were examined after topical administration of the drug. Colitis was induced

by intra-rectal application of oxazolone after previous sensitization. The doses of budesonide used were 25.8 and 129 µg/kg. In oxazolone challenged animals, there were mucosal inflammation of the colon with increased plasma exudation, hyperemia and epithelial permeability. Treatment with 25.8 µg/kg budesonide did not cause any attenuation of the absorptive permeability in the colon while the 129 µg/kg dose caused attenuation of the permeability changes. Budesonide (129 µg/kg) caused significant reductions of the plasma exvasation and abolition of the hyperemia in the oxazolone-challenged animals. Thus, in rats with oxazolone-induced colitis, budesonide reduced the inflammation by decreasing permeability, plasma exvasation, and increased blood flow.

Topical Anticolitic Efficacy and Selectivity of the Glucocorticoid Budesonide in a New Model of Acetic Acid-Induced Acute Colitis in The Rat (Fabia R et al, Aliment Pharmacol Ther 1994; 8: 433441).

The effects of budesonide on acetic acid-induced colitis in Sprague-Dawley rats were examined after local instillation (10^{-6} or 10^{-8} M) or s.c. administration (0.5, 0.75 or 1.0 mg/kg) of the drug. The treatment started on the day after acetic acid instillation and continued on Days 2 and 3. The effect of the drug on the plasma exudation into the colonic lumen was measured using ^{125}I-labeled albumin as a tracer. The animals were sacrificed on the fourth day after colitis induction and the colonic segments were examined microscopically and the tissue myeloperoxidase activity was determined. Acetic acid induced colitis caused significant increases in total morphological scores, tissue myeloperoxidase activity (units/g; one unit was defined as the amount of the enzyme present that produces a change in absorbency at 655 nm per min at 37^0C) and plasma exudation (µL/min/g) into the colonic lumen of the rats as compared with the controls, and treatment with local budesonide caused significant reduction of all the three parameters (total morphological scores:- control 1.5±0.2, acetic acid 14.8±0.8, budesonide 3.5±0.4; myeloperoxidase activity- control 83.8±5.5, acetic acid 258.6±23.4: budesonide 109.1±8.3; plasma exudation- control 0.28±0.05, acetic acid 1.68±0.18, budesonide 0.56±0.08). Subcutaneous budesonide also caused significant improvements of the morphologic scores and the plasma exudation values in acetic acid-induced colitis in rats.

Effects of Local Budesonide Treatment on The Cell Mediated Immune Response in Acute and Relapsing Colitis in Rats (Palmen MJ et al, Dig Dis Sci 1998: 43: 2518-2525).

The effects of budesonide and dexamethasone on acute experimental colitis and on T cells in thymus and spleen were examined in rats. The effect of budesonide was also examined on relapsing colitis in rats. Colitis was induced by intra-colonic administration of trinitrobenzene sulfonic acid (TNBS; 30 mg/animal in ethanol). Relapse was induced 5 weeks after the initial induction of colitis by an intraperitoneal booster dose of TNBS (30 mg/animal in 0.5 ml saline). The glucocorticosteroids (150 µg) were administered intra-rectally on days 1, 4 and 6 after induction of acute colitis or relapse. All TNBS-treated animals developed symptoms of colitis, such as diarrhea and transmural

inflammation with or without ulceration. Treatment with budesonide in acute and relapsing colitis resulted in a reduction of microscopic damage (damage score was reduced from 4.2 to 0.3 and 0.46 on days 13 and 16, respectively) and decreased the numbers of macrophages and neutrophils in the colon. Dexamethasone was less effective than Budesonide. Dexamethasone but not budesonide, reduced the number of T cells in the thymus. Budesonide treatment in relapsing colitis resulted in a mean damage score in the colon (from 0.81 to 0.21). The study suggests that budesonide is more effective than dexamethasone in the treatment of acute experimental colitis in rats and budesonide did not cause general suppression of T cells.

Immunopharmacology of Budesonide-Induced Inhibition of Pro-Inflammatory Cytokine Secretion by IBD Mononuclear Phagocytes (Schreiber S. et al., Gastroenterology 1996; 110: 1011).

The immunopharmacology of budesonide-induced deactivation of peripheral monocytes/intestinal macrophages were examined in biopsy specimens of human intestinal lamina propria in vitro. The inhibition kinetics of the pro-inflammatory cytokines (IL-1β, IL-6, IL-8) and IL-1ra release in culture supernatants were assessed by Northern Blot. Budesonide inhibited the release of proinflammatory cytokines by intestinal lamina propria mononuclear cells (LMPNC) and peripheral monocytes in a dose-dependent manner; no differences were observed between IBD patients and normal subjects. Budesonide was approximately 10 times more potent in inhibiting the pro-inflammatory cytokines than dexamethasone. Treatment of the intestinal LMPNC or monocytes with $5x10^{-5}$ M budesonide caused complete inhibition of the pro-inflammatory cytokine release for up to 60 hours. Thus, there was a prolonged inhibition of the pro-inflammatory cytokines by budesonide, and once daily dosing may be sufficient for the treatment of IBD.

The locally acting glucocorticosteroid budesonide enhances intestinal sugar uptake following intestinal resection in rats. (A Thiesen et al, Gut 2003;52:252–259).

The effect of different glucocorticoids including budesonide was assessed for local intestinal transport in adult Sprague Dawley rats. The middle 50% of the small intestine was removed from half of the animals. The other half of the rats had a transaction; the small intestine was divided and then reanastomosed without removal of any portion of the intestine. The glucocorticosteroids (budesonide, prednisone, and dexamethasone) were given to animals orally with a 50% resection. There were six animals in each of the four treatment groups: control vehicle (0.19% EDTA buffered saline), budesonide (0.25 mg/kg body weight per day), prednisone (0.75 mg/kg body weight/day), and dexamethasone (128 mg/kg body weight/day). As a probe and marker compound, [^{3}H] inulin was used as a non-absorbable marker to correct for the adherent mucosal fluid volume. [^{14}C] labeled probes included varying concentrations of D-glucose and D-fructose (4, 8, 16, 32, and 64 mM). The concentration of L-glucose used was 16 mM.

The 50% enterectomy did not alter jejunal or ileal uptake of glucose or fructose. Prednisone had no effect on the uptake of glucose or fructose in resected animals. In contrast, in resected rats budesonide increased by over 120% the value of the jejunal maximal transport rate for the uptake of glucose, and increased by over 150% ileal uptake of fructose. Protein abundance and mRNA expression of the sodium dependent glucose transporter in brush border membrane (SGLT1), sodium independent fructose transporter in the brush border membrane (GLUT5), sodium independent glucose and fructose transporter in the basolateral and brush border membranes (GLUT2), and Na^+/K^+ ATPase a1 and b1 did not enhance the effect of budesonide on glucose or fructose uptake. Budesonide, prednisone, and dexamethasone reduced jejunal expression of the early response gene c-jun. In resected animals, expression of the mRNA of ornithine decarboxylase (ODC) in the jejunum was reduced, and corticosteroids reduced jejunal expression of the mRNA of proglucagon. These data suggest that the influence of corticosteroids including budesonide on sugar uptake in resected animals may be achieved by post translational processes involving signalling with c-jun, ODC, and proglucagon, or other unknown signals. Thus, the glucose and fructose absorption promoting effect of budesonide following intestinal resection may prove it to be a useful agent to enhance the intestinal adaptive response.

Corticosteroids Modulate the Secretory Processes of the Rat Intrahepatic Biliary Epithelium. (D. Alvaro et al, Gastroenterology, 2002; 122:1058-1069).

Glucocorticoids receptors (GcRs) are expressed by the rat cholangiocytes, which is secreted from intrahepatic biliary epithelium. A major function of the intrahepatic biliary epithelium is bicarbonate excretion in bile, which is mainly driven by the apical Na^+ - independent $Cl^-/HC03^-$ exchanger identified as isoform AE2 in rat and man, and is functionally coupled with the cystic fibrosis transmembrane regulator (CFTR). The expression of glucocorticoid receptors (GcRs) in the intrahepatic biliary epithelium and the role of corticosteroids in the regulation of cholangiocyte secretion were studied by immunohistochemistry, reverse-transcription polymerase chain reaction, and Western blots. The effects of dexamethasone and budesonide on biliary bicarbonate excretion and $H^+/HCO3^-$ transport processes were investigated in bile fistula rats. Male Wister rats with intrahepatic bile fistula received dexamethasone (5 µmol/L for 40-80 min) or budesonide (1 µmol/L for 40-80 min) via jugular vein. After treatment with corticosteroids, bile secretion was monitored and intrahepatic bile duct units (IBDUs) isolated, and cholangiocytes were purified. Acute administration of corticosteroids showed no effect on bile flow and bicarbonate biliary excretion. A 2-day treatment with dexamethasone or budesonide induced a significant increase ($P < 0.05$) in bile flow and biliary excretion of bicarbonate. Bile flow and bicarbonate secretion were blocked after administration of mifepristone (GcR agonist). IBDUs isolated from rats treated with dexamethasone or budesonide showed an increased ($P < 0.05$) activity of the Na^+/H^+ exchanger (NHE1 isoform) and $Cl^-/HCO3^-$ exchanger (AE2 member), which was blocked by mifepristone. Protein expression of NHE1 and AE2 and messenger RNA for NH1, but not AE2 were increased ($P < 0.05$) in isolated cholangiocytes by dexamethasone treatment. It was concluded that the intrahepatic biliary epithelium expresses GcRs and responds to corticosteroids by increasing bicarbonate excretion in

bile. This is caused by corticosteroid-induced enhanced activities and protein expression of transport processes driving bicarbonate excretion in the biliary epithelium.

4.3 Safety Pharmacology

No safety pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

The applicant did not submit any pharmacokinetic studies with budesonide. However, the applicant submitted available published pharmacokinetics studies of budesonide, which are reviewed below:

Budesonide is Metabolized by Cytochrome P450 3A (CYP3A) Enzymes in Human Liver (Jonsson G et al, Drug Metab Disp 1995; 23(1): 137-42).

To identify the isoform of cytochrome P450 involved in the metabolism of budesonide, budesonide was incubated with microsomes from ten different human liver samples where the different CYP activities had been rank ordered. A strong correlation between the formation of the two budesonide metabolites, 16α-hydroxy prednisolone and 6β-hydroxybudesonide and testosterone 6β-hydroxylation (a marker of CYP3A) was observed (R=0.98 and 0.95). When budesonide was incubated with the human liver microsomes in the presence of compounds that interact with different isoforms of CYP, ketokonazole was found to be the strongest inhibitor of budesonide metabolism (IC_{50} ~ 1 μM) followed by troleandomycin (IC_{50}~1 μM), erythromycin and cyclosporine, all substances known to be metabolized by CYP3A. Substances known to be metabolized by CYP2C (sulfaphenazole, mephenytoin and tolbutamide and CYP2D6 (Quinidine) did not specifically inhibit the metabolism of budesonide. The formation of the budesonide metabolites was also inhibited by CYP3A antibody but not by CYPIA antibody or control immunoglobulin G, thus confirming that budesonide is metabolized by CYP3A subfamily of enzymes.

Pharmacokinetics of budesonide and its major ester metabolite after inhalation and intravenous administration of budesonide in the rat. (Jendbro M et al, Drug Metabolism and Disposition, 2001: 2905-769–776).

Pharmacokinetics of budesonide and budesonide-fatty acid esters (oleates) was examined following both inhalation and i.v. administration in the rat. For inhalation administration of budesonide, micronized dry powder was administered by inhalation to rats using an aerosol delivery system adapted for small animals. The inhaled dose was 210 nmol/kg. The rats were put in restraining tubes connected to the inhalation chamber and exposed to BUD for approximately 10 min. Groups of 3 rats were sacrificed at 15, 30, 45, 60, and 90 min and 2, 4, 8, 12, and 24 h after start of the inhalation. Plasma, lungs, and trachea were collected at all time points.

Male Sprague-Dawley rats were administered [^{3}H]-budesonide intravenously (tail vein) at an approximate dose of 7 µg/kg (16 nmol/kg). Groups of 3 animals were sacrificed at each of the following time points and plasma samples were obtained at 5, 15, 30, 45, and 60 minutes, 1.5, 2, 4, 8, 12 and 24 h after budesonide administration. Samples of lung, trachea and muscle tissues were collected for radioactivity analysis of [^{3}H]-budesonide. Levels of both [^{3}H]-budesonide and [^{3}H]-budesonide-oleate were determined in both plasma and tissues.

After inhalation, budesonide half-life was longer (8.2 h) in trachea than in plasma (3.7 h), with similar data after intravenous dosing. Results are presented in the Table below. Following i.v. dosing, a half-life of 4.7 hours and $AUC_{(0\text{-inf})}$ of 1.59 µg.h/L were obtained for budesonide, and budesonide-oleate exhibited a half-life of 5.4 hours and an $AUC_{(0\text{-inf})}$ of 0.56 µg.h/L. A plasma clearance of 4.4 L/hr/kg was determined for budesonide. In the tissues tested for radioactivity, exposure of the tissues was notably higher than that of the plasma. For comparison, the AUC values, indicative of total exposure over time, for the lung, trachea and muscle were 14.7, 10.1 and 6.06 µg.h/L, respectively, compared to the value of 1.59 µg.h/L obtained for plasma following i.v. administration. Formation of budesonide-oleate occurred in all tissues, and concentrations of the oleate form of the compound decayed in a bi-phasic pattern over time. This study confirmed that fatty ester esterification represents a common mechanism for metabolism and ultimately storage of steroid hormones.

PXR-mediated induction of human CYP3A4 and mouse Cyp3 all by the glucocorticoid budesonide. (Zimmermann, C. et al, Eur. J. Pharm. Sci, 36 (2009) 565-571).

Budesonide is metabolized by cytochrome P450 3A4 (CYP3A4). Inhibition or induction of CYP3A4 could cause drug-drug interactions. Thus, CYP3A4 activity was assessed by the metabolism of a luminogenic substrate (luciferin-benzylether) using recombinant human CYP3A4 protein. There was no inhibition of the metabolism in the presence of budesonide at concentrations up to 25 µM. Induction experiments in human LS180 colon carcinoma cells showed an increased expression of CYP3A4 mRNA after budesonide treatment. Transactivation assays revealed that budesonide activates the CYP3A4 promoter via the pregnane X receptor (PXR). In mice, oral budesonide administration (25 mg/kg) for 4 days induced 3-fold murine homolog Cyp3a11 in the intestine, whereas liver expression was markedly less influenced. In knockout mice devoid of PXR, budesonide-mediated inductions were significantly reduced compared to wild-type mice. In conclusion, budesonide is not an efficient inhibitor but rather an inducer of CYP3A via a PXR-mediated mechanism. However, oral administration of budesonide to mice showed only modest gene induction, which occurred mainly in the intestine. Thus, the risk for budesonide-mediated drug interactions seems to be low but cannot be ruled out entirely.

6 General Toxicology

No single- or repeated-dose toxicology study reports were submitted. However, upon Agency's request the applicant conducted a 28-day repeated-dose oral toxicology study with budesonide MMX tablets in monkeys to compare the toxicology and toxicokinetics of Budesonide MMX and Entocort® EC, and the final report of the study was submitted.

6.1 Single-Dose Toxicity

N/A

6.2 Repeat-Dose Toxicity

Study title: CB-01-02 - Budesonide MMX™ 9 mg extended release tablets: A 28-day oral toxicity study in Cynomolgus monkeys followed by a 14-day recovery period.

Study no.:	1006-1893
Study report location:	Electronic submission (EDR)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 6, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Budesonide MMX: Lot # 5970/2 and purity >95% Entocort: Lot # MK0124, MF0078

Key Study Findings

Oral administration of CB-01-02 - BUDESONIDE MMX™ 9 MG tablets or Entocort 3 mg capsules at 18 mg/day for 28 days to Cynomolgus monkeys was well-tolerated. No treatment-related adverse effects or significant inter-group differences in the evaluated study parameters were observed in animals receiving both treatments. The extent of budesonide bioavailability from CB-01-02 - BUDESONIDE MMX™ 9 MG tablets (9 mg X 2) was less than that from Entocort 3 mg capsules (3 mg X 6) on Days 1 and 28. In addition, the rate of absorption from the tablets was slower than that from the capsules on both Days 1 and 28.

Methods

Doses:	Budesonide 18 mg Tab and Entecort 18 mg Cap.
Frequency of dosing:	Once daily
Route of administration:	Oral
Dose volume:	Budesonide 2 Tabs and Entecort 6 Caps
Formulation/Vehicle:	N/A
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3/sex/dose group
Age:	3-5 years
Weight:	Males - 3.5 to 4.2 kg and females - 2.5 to 3.3 kg
Satellite groups:	No
Unique study design:	None
Deviation from study protocol:	None

Observations and Results

Mortality

Animals were checked twice daily for mortality.

There was no mortality. All animals survived at the end of the study.

Clinical Signs

Cage-side observations of clinical signs were performed once daily throughout the study. A detailed clinical examination was performed on each animal once upon arrival, prior to randomization and once weekly starting one week prior to initiation of treatment.

There were no treatment-related clinical signs during the study.

Body Weights

Body weights were recorded for all animals once prior to randomization and one a week prior to the initiation of treatment. During the treatment and recovery periods, body weights were recorded once weekly, including one day prior to initiation of dosing and one day prior to necropsy.

There was no effect on body weight changes that might be considered related to the treatment with the CB-01-02 - BUDESONIDE MMXTM 9 MG tablets or Entocort 3 mg capsules.

Feed Consumption

Food intake was determined daily.

Food intake was not affected by the treatment.

Ophthalmoscopy

Funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit-lamp) examinations were performed on both eyes of all animals, following the application of a mydriatic agent, once prior to the initiation of treatment, and near the end of Week 4 of the treatment period.

Budesonide did not cause any adverse ocular effects.

ECG

Electrocardiograms (leads I, II and III, and augmented leads aVR, aVL and aVF) were obtained for all animals once during the pre-treatment period and once near the end of Week 4 of the treatment period. ECG tracings were assessed for gross changes indicative of cardiac electrical abnormalities. Heart rate (lead II), rhythm, and conduction abnormalities were also evaluated.

Administration of budenoside or entocort had no effect on the morphology of the ECG complexes, heart rates or intervals of the ECG of Cynomolgus monkeys.

Hematology

Blood samples were collected by venipuncture of one of the femoral veins. Food and water were removed overnight prior to blood collection. Hematology examination was performed for all animals once during the pre-treatment period, towards the end of Week 4 of the treatment period (Day 29), and towards the end of the Recovery period (Day 15 of Recovery period). Following hematological parameters were determined.

Parameters Examined

Red blood cell count	Mean Corpuscular Hemoglobin
Hematocrit	Mean Corpuscular Hemoglobin
Hemoglobin	Concentration
Hemoglobin Distribution Width	Mean Corpuscular Volume
White blood cell count	Platelet count
WBC differential (absolute and relative)	Plateletcrit/Thrombocrit
Reticulocyte count (absolute and relative)	Red Cell Distribution Width

* K_3EDTA was used as an anticoagulant.

Coagulation*

Parameters Examined

Activated partial thromboplastin time
Prothrombin time

No treatment-related effects were observed in hematological and coagulation parameters. At the end of the treatment period, some leukocyte parameters (lymphocytes, eosinophils, basophils) were statistically elevated in Group 2 males (Entocort 3 mg capsules), as compared to Group 1 but the values were comparable to pre-treatment results or were within the range of normal variation for similar populations of Cynomolgus monkeys. Results are presented in the Table below.

GROUP 1: CB-01-02-Budesonide MMX™ (18 mg) - 2 tablets
GROUP 2: Reference Article (Entocort 18 mg) - 6 capsules

GROUP NO.		NEUT $x10^9/L$	LYMPH $x10^9/L$	MONO $x10^9/L$	EOS $x10^9/L$	BASO $x10^9/L$	NEUT %	LYMPH %	MONO %	EOS %	BASO %
MALES											
1	MEAN	9.75	3.87	0.28	0.02	0.05	66.5	30.5	2.1	0.2	0.3
	SD	4.964	1.054	0.047	0.034	0.024	15.78	14.66	0.73	0.34	0.10
	N	4	4	4	4	4	4	4	4	4	4
2	MEAN	8.78	7.16 *	0.50	0.16 *	0.09 *	51.3	43.7	2.9	1.0	0.5 *
	SD	3.491	1.995	0.191	0.091	0.013	14.45	14.35	0.81	0.59	0.08
	N	4	4	4	4	4	4	4	4	4	4
FEMALES											
1	MEAN	8.74	3.61	0.37	0.06	0.05	67.7	28.4	2.9	0.4	0.4
	SD	1.976	0.995	0.111	0.071	0.006	8.59	8.06	0.65	0.54	0.05
	N	4	4	4	4	4	4	4	4	4	4
2	MEAN	9.02	3.89	0.50	0.11	0.05	61.7	32.5	4.0	1.0	0.4
	SD	5.158	0.683	0.123	0.072	0.015	16.87	14.75	1.46	0.90	0.06
	N	4	4	4	4	4	4	4	4	4	4

*: Statistically significant when compared with Group 1 at $p \leq 0.05$

Clinical Chemistry

Clinical chemistry determination was performed for all animals once during the pre-treatment period, towards the end of Week 4 of the treatment period (Day 29), and towards the end of the Recovery period (Day 15 of Recovery period). Following clinical chemistry parameters were determined.

Parameters Examined

A/G ratio (calculated)
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Bilirubin(total)
Calcium
Chloride
Cholesterol (total)
Creatinine
γ-Glutamyl transferase
Globulin (calculated)
Glucose
Phosphorus (inorganic)
Potassium
Sodium
Total protein
Triglycerides
Urea

For cortisol analysis, blood samples were collected in the morning, between 8:00 and 10:00 AM.

There were no adverse effects on clinical chemistry parameters after administration of budesonide MMX™ 9 MG tablets or Entocort 3 mg capsules.

Regarding cortisol analysis, at the end of the treatment period, there were no evidences of adrenal suppression in both treated groups.

Urinalysis

Urine analysis was conducted once during the pre-treatment period, towards the end of Week 4 of the treatment period (Day 29), and towards the end of the Recovery period (Day 15 of Recovery period). Following parameters were determined.

Parameters Examined

Bilirubin	Protein
Blood	Specific gravity
Color and appearance	Urine sediment
Glucose	Urobilinogen
Ketones	Volume
pH	

No treatment-related adverse effects were noticed on urinalysis parameters.

Gross Pathology

Animals were euthanized on Day 29 and Recovery animals were euthanized on Recovery Day 15 (i.e. approximately 2 weeks following the last day of treatment) following an overnight period without food and/or water. For all animals, gross pathology consisted of an external examination, identification of all clinically-recorded lesions, as well as a detailed internal examination.

There were no treatment-related macroscopic pathological changes noted at necropsy.

Organ Weights

For all animals, the following organs were dissected, trimmed free of fat and weighed:

Adrenals	Testes
Brain	Pituitary
Heart	Prostate
Kidneys	Spleen
Liver	Thymus
Lungs	Thyroids and Parathyroids
Ovaries	Uterus

In both dosing groups (budesonide and Entocort), some individual males and females showed low absolute and relative weight of the thymus compared to the other animals. However, these weights were similar in mean absolute organ weight and % of body weight.

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings

On completion of the gross pathology examination, the following tissues and organs were retained from all animals. Neutral buffered 10% formalin was used for fixation and preservation.

Abnormal tissues/lesions	Pituitary
Adrenals	Prostate
Animal Identification *	Salivary Gland (Mandibular)
Aorta (Thoracic)	Sciatic Nerve
Brain	Seminal Vesicles
Cecum	Skeletal Muscle
Colon (Ascending, descending and transverse)	Skin & Subcutis (Thoracic)
Epididymides	Small Intestine, Duodenum
Esophagus	Small Intestine, Ileum
Eyes	Small Intestine, Jejunum
Femur & Marrow	Spinal Cord (Cervical)
Gallbladder	Spleen
Heart **	Sternum & Marrow
Kidneys	Stomach (Cardia, pylorus and fundus)
Liver (2 lobes)	Testes
Lungs (2 lobes with Bronchi) ***	Thymus
Lymph Node, Mandibular	Thyroids & Parathyroids
Lymph Node, Mesenteric	Tongue
Mammary Gland (Thoracic)	Trachea
Optic Nerves	Urinary bladder
Ovaries	Uterus
Pancreas	Vagina

* Fixation and preservation only.
** Section including both ventricles and atria, septum with papillary muscle.
*** Lungs were infused with formalin.

However, histopathological examination was performed on the list of tissues presented below. Tissues were prepared for histological examination by embedding in paraffin wax, sectioning and staining with hematoxylin and eosin.

Stomach (Cardia, pylorus and fundus)
Heart
Colon (Ascending, descending and transverse)
Kidneys
Liver
Lungs with trachea
Small Intestine, Ileum, duodenum and jejunum
Spleen
Adrenals
Pituitary
Thymus
Any abnormal tissues/lesions

There were no histopathological findings suggestive of treatment-related tissue toxicity in this study. However, animals in both groups exhibited minimal to mild thymic lymphoid hypocellularity/atrophy. This sometimes correlated with gross findings of small thymus and/or reduced thymus weight. The incidence of these findings was low and comparable between the two groups.

Special Evaluation

None

Toxicokinetics

Blood samples (approximately 2.0 mL) were collected from all animals on Days 1 and 28 at the following time points at pre-dose and at 1, 3, 6, 9, 12, 16 and 24 hr post-dose.

The pharmacokinetic profiles and systemic exposure of budesonide tablets are different from budesonide capsules after single (Day 1) and 28-day repeated administration in Cynomolgus monkeys. The bioavailability of budesonide tablets was less than that of Entocort capsules. The mean peak exposure (C_{max}) and total exposure ($AUC_{(0-24)}$) of budesonide for the tablets were half or less than half of those for the capsules in females. In males, C_{max} and $AUC_{(0-24}$ of budesonide tablets were more than 4-fold when compared to capsules.

In addition, the rate of absorption from the tablets was slower than that from the capsules after both single and 28-days repeated administration. The T_{max} of budesonide tablets was longer than that in the capsules in both males and females.

It appeared that female animals had higher mean peak and total exposures when compared to their male counter parts for both the test (tablets) and reference (capsules) formulations on Days 1 and 28. Toxicokinetic data are presented in the Table below.

Table: Toxicokinetic parameters of budesonide tablets and entocort capsules on Days 1 and 28 in cynomolgus monkeys following daily oral administration.

Treatment	Day	Sex	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24} hr*ng/mL
Entecort Capsule	1	Female	7.38±3.03	3.0±0	48.13±9.08
		Male	4.85±2.87	6.0±0	40.27±19.32
	28	Female	6.26±2.82	4.5±1.7	40.47±15.58
		Male	3.99±3.80	5.25±1.5	28.80±21.88
Budesonide MMX Tablet	1	Female	3.32±3.2	14.50±7.14	25.65±21.49
		Male	0.92±1.07	12.50±4.94	9.79±11.49
	28	Female	3.06±2.09	15.75±9.60	21.87±12.64
		Male	0.89±0.21	10.00±12.49	11.78±3.05

7 Genetic Toxicology

No genetic toxicology studies were submitted.

8 Carcinogenicity

No carcinogenicity studies were submitted.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted.

10 Special Toxicology Studies

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

In the current submission, the applicant is seeking approval of budesonide MMX tablets (UCERIS) for the treatment of mild to moderate UC. UCERIS is a delayed release tablet formulation containing 9 mg of budesonide. The recommended oral dose is one tablet daily in the morning for up to 8 weeks.

Budesonide is a synthetic glucocorticoid with high topical anti-inflammatory activity, with limited systemic adverse effects. Budesonide has been shown to exhibit significant anti-inflammatory activity in the lower GI tract. Budesonide (Entocort® EC) is currently approved for the treatment of CD. Budesonide has strong glucocorticoid receptor (GCR) affinity and an effective first pass metabolism by the liver with a short half-life.

In this 505 (b)(2) NDA, the applicant relied on the Agency's previous assessment of safety of budesonide. In addition, as per the Agency's recommendation, a 28-day repeated dose oral toxicity study in Cynomolgus monkeys was conducted and the final study report was submitted in the NDA. The applicant also provided available published nonclinical studies of budesonide.. The published studies showed that budesonide is an effective anti-inflammatory agent through modulation of translation of NF-κB. Budesonide also causes inhibition of cytokine release from MHC-1. Cytochrome P450 3A (CYP3A) plays a key role in the metabolism of budesonide.

A 28-day repeated dose toxicity study of budesonide was conducted in Cynomolgus monkeys. There was no overt clinical reactions or serious toxicity in monkeys treated orally with budesonide at 18 mg/day once daily for 28 days.

In conclusion, budesonide has a long history of use in humans. Budesonide (Entocort®) was approved for marketing in 2001 for the treatment of mild to moderate CD involving the ileum and or the ascending colon. In this NDA, the applicant is seeking approval of the 9 mg dose, which is a approved dose of budesonide. This NDA is submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and the applicant relied upon the Agency's previous findings and publicly available information on budesonide. In addition, 28-day toxicology bridging study in monkeys submitted by the applicant showed no overt clinical findings and serious toxicity at an oral dose of 18 mg/day. Thus, there are no safety concerns for the proposed dose of budesonide in the proposed patient population in the proposed dosage form.

12 Appendix/Attachments: None

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/s/

DINESH C GAUTAM
10/15/2012

SUSHANTA K CHAKDER
10/15/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203-634 **Applicant: Santarus Inc.** **Stamp Date: December 16, 2011**

Drug Name: Uceris (Budesonide MMX) **NDA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Yes		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Yes		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Yes		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Yes		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Yes		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	Yes		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	Yes		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Yes		Upon Division's request (June 8, 2006), a 28-day oral toxicity study in cynomolgus monkeys followed by a 14-day recovery

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
				period is submitted with the application.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	Yes		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Yes		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __ YES___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Dinesh Gautam, Ph.D

Reviewing Pharmacologist Date

Sushanta Chakder, Ph.D

Team Leader/Supervisor Date

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

/s/

DINESH C GAUTAM
01/18/2012

SUSHANTA K CHAKDER
01/18/2012