CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-324

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-324**	**Brand Name**	**Entocort**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Budesonide**
Medical Division	**DGICDP**	**Drug Class**	**Glucocorticosteroid**
OCPB Reviewer	**Sandip Roy**	**Indication(s)**	**Treatment of mild to moderate active Crohn's disease involving ileum**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Capsules**
		Dosing Regimen	**9 mg QD**
Date of Submission	**1/24/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**6/11/01**	**Sponsor**	**Astra Zeneca**
PDUFA Due Date	**7/24/01**	**Priority Classification**	**3P**
Division Due Date	**6/25/01**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	5		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:		2		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:		6		
In-vivo effects of primary drug:		1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		
PD:				
Phase 2:				

Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	1		
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:	X	2		
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				Requested Deferral
Literature References				
Total Number of Studies	[redacted]	21		

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	(1) Is the delayed + extended release characteristics of the dosage form adequately characterized? (2) Is there a concentration-response relationship for the systemic steroid effects? (3) Is the in vitro release method and proposed specifications adequate to describe the in vitro release profile of the product?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Sandip K. Roy, 6/21/01** **Filing only- Suresh Doddapaneni, 2/26/01**	
Secondary reviewer Signature and Date	**Suresh Doddapaneni, 6/21/01**	

CC: NDA 21-324, HFD-850(Electronic Entry or Lee), HFD-180(McNeil), HFD-870(Doddapaneni, Malinowski, Hunt), CDR (B. Murphy)

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-324			
Submission(s):	Type: 3P	Suppl.: 000	Letter Date: 1/24/01	Date Received: 1/24/01
Reviewer:	Sandip K. Roy, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Budesonide			
Other Name(s):				
Trade Name:	ENTOCORT (proposed)			
Molecular Weight:	430.5			
Molecular Formula:	$C_{25}H_{34}O_6$			
Relevant IND(s)/NDA(s):	NDA 20-233 & 20-746 (Rhinocort), NDA 20-441 & 20-929 (Pulmicort)			
Drug Class:	Glucocorticoid			
Dosage Form:	Modified release capsules			
Route of Administration:	Oral			
Dosing Regimen:	9 mg taken once daily in the morning for up to 8 weeks			
Sponsor:	AstraZeneca			
Proposed Indication:	Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon			

Abbreviations

CDAI: Crohn's Disease Activity Index
CIR: Controlled Ileal Release

SYNOPSIS

ENTOCORT is 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 ascending colon. The site of uptake of budesonide was studied using the technique . The transit of the pellets through the GI tract was followed up to 72 hr, using ^{111}In-labelled pellets as a tracer. The sponsor relied on this method in several studies to estimate that 40 – 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 rational 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. This 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. 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 – 6.0 hrs. Safety data was collected as plasma and urinary cortisol suppression, which is a marker of HPA axis function. Extent of cortisol suppression often correlated well with pharmacokinetic parameters. Dose adjustment in the label was recommended based on safety concern 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).

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

Comments 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 shows 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 hrs.

- In the nethod used to study the site of uptake of budesonide, no rational 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 pH > 5.5, it is not likely that delayed release will last until the ileum. There is published data in fasting subjects indicating pH in stomach and duodenum at 5.5 and it goes down after ingestion of food, or upon passage into the jejunum.

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

7/2/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 21-324
/HFD-180 (Division files, MMcNeil)
/HFD-870 (SDoddapaneni, HMalinowski, SRoy)
/HFD-850 (Plee, LLesko)
/CDR (ZZadeng)

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Overall Summary of
Clinical Pharmacology and Biopharmaceutics Findings

- After oral administration of micronized [^{3}H]-budesonide, 60% of the recovered radioactivity was found in urine [Report No. 850-CR-0047/2], which is close to 63% recovered in urine following IV administration. This indicates that a major portion of the orally administered compound is absorbed as such or as metabolites.
- Prolonged-release capsules of budesonide, consisting of small pellets <1.4 mm in diameter, were tested for the treatment of Crohn's disease located to the ileum and/or the ascending colon. The pellets are designed to release the gastric juice and to continuously release budesonide during passage through the small intestine and the ascending colon.
- About 40 – 70% of the total, systemically available budesonide dose was absorbed in the ileum and the ascending colon (Gut scintigraphy technique used to determine site and extent of absorption is questionable).
- Cumulative amounts of budesonide obtained in the effluent of ileostomy-operated subjects were approximately 6 times higher when budesonide was given as CIR compared to plain capsules. This data indicated that the release of budesonide from CIR formulation is delayed and/or prolonged compared to micronized budesonide in plain capsules.
- After oral dosing of budesonide, the systemic availability is between ' , and the peak plasma concentration is generally reached within 3 hrs. Absorption appears to be complete.
- Systemic exposure of budesonide after administration of budesonide CIR seems to be higher in patients with active Crohn's disease than in healthy subjects. (Mean C_{max} and AUC after a single dose of 4.5 mg was similar to double dose of 9 mg in healthy volunteers).
- Reason for the high plasma peak (C_{max}) in patients with active Crohn's disease after a single dose could be that it may be easier for the drug to penetrate over to the blood in the diseased area (injured intestinal epithelial barrier and an increased blood perfusion may contributing factors)
- Higher AUC in patients with active Crohn's disease cannot be explained by presence of the disease because absorption is probably complete in healthy subjects. (Concomitant food may impair the first pass biotransformation of budesonide after higher dose of the drug; in the disease state, intestinal mucosal permeability is generally more or less abnormal and the liver may be exposed to toxins and the low-molecular compounds and macro-molecules which could also inhibit budesonide first-pass metabolism).
- After repeated dosing of budesonide CIR capsules, plasma concentrations of budesonide increased linearly with dose within the investigated dose range '
- Absorption from CIR budesonide capsule was delayed in presence of food but was still complete or almost complete.
- Systemic availability of orally administered budesonide was 2.5-fold higher in patients with liver cirrhosis compared with healthy controls.
- Omeprazole did not have a significant effect on the pharmacokinetics and systemic effects of budesonide CIR capsules.
- Pharmacokinetic data showed lower AUC and C_{max} values of budesonide after 8 weeks treatment than after a single dose (indicating no accumulation).
- Co-administration of ketoconazole resulted in a 8-fold increase in AUC of budesonide, compared to budesonide alone. When ketoconazole and budesonide were administered 12 hrs apart, the increase of AUC was only 4-fold.
- Although pharmacokinetics of IV budesonide was not affected by cimetidine, C_{max} and systemic availability was slightly higher after oral budesonide during cimetidine treatment. This indicated that the rate of absorption of budesonide was slightly affected by cimetidine. After oral administration of budesonide cortisol suppression was significant only when taken with cimetidine.
- Pharmacokinetics of budesonide was not significantly affected by Desolett, an oral contraceptive. Cortisol suppression was also not affected.

Question Based Review

Background

- **What are the highlights of chemistry, formulation and physicochemical properties of the drug and drug product?**
- **What is the mechanism of action, proposed indication and main goal of therapy?**
- **What are other drugs available in this class?**
- **What are some highlights of claims for this product in the proposed label?**

Chemistry, formulation and physicochemical properties

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

ENTOCORT is supplied as modified-release granules in hard gelatin capsules for oral administration. Each capsule contains 3 mg of budesonide in the form of gastro-resistant, delayed and extended release granules with the following ingredients:

Micronized budesonide (3 mg)
Ethylcellulose
Acetyltributyl citrate
Methacrylic acid copolymer type C
Triethyl citrate
Antifoam M
Polysorbate 80
Talc
Sugar spheres

Mechanism of action, proposed indication and main goal of therapy

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. Budesonide reportedly has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol. Because of substantial first-pass elimination (85 – 90% cleared by hepatic biotransformation), budesonide has a low oral bioavailability.

ENTOCORT is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. To ascertain topical delivery to the ileum and ascending colon, the primary target site for treatment of Crohn's disease, capsules with gastro-resistant granules exhibiting modified-release properties were developed. The gastro-resistant coating is supposed to protect the granules from the gastric juice but dissolve at pH > 5.5, i.e., normally when the granules reach the duodenum. Thereafter, a matrix of ethylcellulose with budesonide is supposed to control the release of the drug into the intestinal lumen in a time-dependent manner.

Other drugs in this class

Glucocorticosteroids (prednisone and prednisolone)
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 TNF)
Non-glucocorticosteroid therapy.

Broad-spectrum antibiotics, immunosuppressives, such as azathioprine and 6-mercaptopurine, and 5-aminosalicylic acid used to treat active Crohn's disease, but not approved.

Budesonide is also approved in USA for the following products: Rhinocort Nasal Inhaler, Pulmicort Turbuhaler, Rhinocort Aqua Nasal Spray, and Pulmicort Respules. The indications are as follows:

Rhinocort: Management of nasal symptoms of seasonal or perennial allergic rhinitis
Pulmicort: Maintenance treatment of asthma as prophylactic therapy

Highlights of claims

- Localized release at the site of inflammation [gastro-resistant, delayed and extended release]
- Little systemic bioavailability
- Minimal suppression of adrenal function
- Small or no impact on other organ systems and metabolic function
- Efficacy similar to conventional steroids

Following ADME information relevant for this NDA is taken from package insert for Rhinocort earlier approved by the FDA:

- In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer.
- *In vitro* studies indicated that the two forms of budesonide do not interconvert.
- Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 3A isoenzyme-catalyzed biotransformation.
- The 22R form was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form.
- The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

- **Is the delayed + extended release characteristics of the dosage form adequately characterized in both patients and healthy volunteers?**

Entocort (Budesonide) capsule does not exhibit delayed release characteristics in a consistent manner and the dosage formulation does not appear to be reliable. 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 (Appendix II). 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 – 6.0 hrs (Appendix III).

- Absorption of budesonide from CIR capsules in different parts of gastrointestinal tract varied greatly between patients.
- Budesonide CIR pellets formulation is more slowly absorbed in patients with Crohn's disease than plain micronized ($^2H_8$) budesonide (MRT of 8 hr vs 6 hr at the dose of 4.5 mg).
- Considerably more of plain ($^2H_8$) budesonide seemed to have been absorbed in stomach (40 – 50%) as compared to less than 15% after administration of CIR pellets.
- In Study 08-0204, in healthy volunteers ~70% of the absorption occurred in the ileum and ascending colon at the dose of 18 mg, whereas in patients with Crohn's disease only ~43% of the absorption occurred in the same region.
- In Study 08-3029, 58 & 52% of the absorbed dose was absorbed in the ileum and ascending colon in healthy volunteers at the dose of 4.5 mg before and after heavy breakfast, respectively.
- Gastric emptying was delayed by the presence of food in the stomach, but the absorption was still complete or almost complete.
- In patients with Crohn's disease, only 17% of the dose was absorbed in the ileum at the dose of 18 mg and ~25% at the dose of 4.5 mg in healthy volunteers (vs 20% with plain budesonide). Based on these data and since this was not investigated at the dose of 9.0 mg, it is probably not appropriate to refer to these pellets as Controlled Ileal Release (CIR) pellets.
- As summarized in Appendix IV table, pharmacokinetic parameters (C_{max}, T_{max}, and AUC) for CIR capsules varied considerably between studies and in some studies the values obtained were similar to capsules containing plain budesonide mixed with lactose. In studies (Report # 850-CR-3029 & 850-CR-7018/B) where patients were given budesonide CIR pellets together with plain budesonide, there was a considerable difference in T_{max} values between CIR pellets and plain ($^2H_8$) budesonide (4.5 – 8.0 vs 1.8 – 3.5). In one study (Report # 850-CR-3015), there was no difference in AUC, C_{max}, and T_{max} between plain and CIR capsules. In another study (Report # 850-CR-3019), T_{max} values ranged between 2.3 to 3.1 hrs for CIR capsules which is similar to values obtained with capsules containing plain budesonide mixed with lactose. The sponsor explained for one study (Report # 850-CR-3015) that the buoyant density of the capsule is much lower for plain budesonide as compared to budesonide mixed with lactose and it probably float to the surface of the ventricular contents before they are dissolved. In addition, budesonide is a lipophilic substance and agglomeration and agglomeration may occur, whereas when mixed with lactose the particles spread more easily facilitating dissolution.
- In a study conducted in ileostomy-operated subjects, the cumulative amounts of budesonide obtained in the effluent were approximately 6 times higher when budesonide was given as CIR compared to plain capsules indicating that the release of budesonide from CIR formulation is delayed and/or prolonged.

Budesonide CIR Pellets [Study No. 08-0204]

The rate, extent and site of absorption of budesonide released from controlled ileal release (CIR) pellets were determined in healthy volunteers [Report 850-CR-7018/A3] as well as in patients with Crohn's disease [Report 850-CR-7018/B] in the ileum or the ileum plus the ascending colon. Each patient was given 18 mg budesonide CIR pellets. The transit of the pellets through the GI tract was followed by gamma scintigraphy up to 72 hr after oral administration, using ^{111}In-labelled pellets as a tracer. The outlining of the stomach was visualized by the co-administration of a ^{99m}Tc-colloid. The cumulative absorption profiles were assessed by deconvolution, using mean intravenous plasma concentration data obtained from a previous study and by scaling to percent of the dose absorbed within 24 hrs. Through the combination of intestinal transit and pharmacokinetic data, and assuming prompt transmucosal diffusion, the fraction of totally absorbed drug was then estimated in different regions of the gut.

Following table shows:

Absorption of CIR budesonide in different parts of the GI tract (expressed as % of totally absorbed dose)

Parts of GI tract	Crohn's Disease	Healthy volunteers	
		Fasting	After heavy breakfast
GE*	15.9 ± 9.2	2.6 ± 3.2	9.8 ± 13.7
Small Intestine	32.8 ± 24.0	48.4 ± 22.6	51.2 ± 28.4
Ileum	17.2 ± 11.4	26.6 ± 12.0	32.2 ± 17.1
Ascending colon	25.3 ± 26.1	41.8 ± 14.4	36.9 ± 26.2
Ileum + Ascending colon	42.5 ± 30.1	68.4 ± 10.1	69.1 ± 17.6
Rest of colon	26.0 ± 36.9	6.9 ± 13.6	1.9 ± 2.2

*Absorption of budesonide when 50% of Indium pellets had been emptied from the stomach

Pharmacokinetic parameters for CIR budesonide and plain ($^2H_8$) budesonide

Parameter	Crohn's Disease		Healthy volunteers	
	CIR Budesonide	plain ($^2H_8$) budesonide	Fasting	After heavy Breakfast
C_{max} (nmol/L)*	14.3 (83)	14.7 (45)	5.8	9.1
F (%)*	20.5 (48)	21.4 (38)	9.1	11.5
MAT (hr)#	9.0 (2.3)	5.5 (0.9)	5.8	6.4
T_{max} (hr)+	8.0 (6 – 16)	3.5 (2 – 4)	3.1 (2 – 6)	5.4 (3 – 8)

*values are expressed as mean (CV%)
#values are expressed as mean (SD)
+values are expressed as mean (range)

Budesonide CIR Capsules Healthy Volunteers [Study No. 08-3029]

Gastrointestinal transit and pharmacokinetics of capsules containing 4.5 mg budesonide CIR pellets were also investigated just before or after breakfast in healthy male volunteers. The results were compared with those after simultaneous intake of a capsule of plain 4.5 mg ($^2H_8$) budesonide mixed with lactose. Following table shows:

Absorption of budesonide in different parts of the GI tract (expressed as % of totally absorbed dose)

Parts of GI tract	Capsule with CIR pellets		Capsule with plain budesonide	
	Before meal	After meal	Before meal	After meal
GE	9.2 ± 5.8	12.4 ± 6.6	35.7 ± 19.4	46.8 ± 15.9
Small Intestine	53.9 ± 25.0	46.7 ± 23.3	48.0 ± 16.1	38.3 ± 18.3
Ileum	24.0 ± 8.2	24.5 ± 8.2	19.6 ± 11.4	15.2 ± 7.2
Ascending colon	34.3 ± 26.3	28.0 ± 19.9	14.6 ± 9.4	10.1 ± 5.2
Ileum + Ascending colon	58.3 ± 23.2	52.5 ± 18.2	34.2 ± 18.0	25.3 ± 10.8
Rest of colon	12.9 ± 2.6	12.7 ± 20.7	1.7 ± 2.1	4.8 ± 5.3

Pharmacokinetics summarized as arithmetic means (range)

Parameters	Capsule with CIR pellets		Capsule with plain budesonide	
	Before meal	After meal	Before meal	After meal
T_{max} (hr)	4.5 (3 – 6)	5.2	1.8	2.9
MRT (hr)	7.8	8.0	6.0	6.4
C_{max} (nmol/L)	2.6	2.7	3.3	2.8
AUC (nmol/L.hr)	18.0	16.9	18.0	18.5

Budesonide CIR Capsules in Patients with Crohn's Disease [Study No. SD-051-3029]

Comparison between patients with Crohn Disease and Healthy Volunteers

Parameters	Crohn's Disease (9 mg)		Healthy Volunteers (4.5 mg)	
	Fasting	After Heavy Breakfast	Before meal	After meal
T_{max} (hr)	3.75	6.25	4.5	5.2
MRT (hr)	7.0	9.3	7.8	8.0
C_{max} (nmol/L)	5.0	4.5	2.6	2.7
AUC (nmol/L.hr)	31.2	30.7	18.0	16.9

Study 08-0204:

Healthy Volunteers
This study was of an open design in 8 healthy male volunteers. An oral dose of 18 mg budesonide CIR together with 3 MBq ^{111}In pellets administered on two different occasions, in a fasting state and immediately after a heavy breakfast. Blood samples were taken during 72 hr in 4 subjects and during 24 hr in another 4 subjects for assessment of budesonide pharmacokinetics. IV data on budesonide were used to estimate the rate and extent of systemic availability.

Patients with Crohn's Disease
This study was of an open design. Six patients (3 men and 3 women) were included in the study
Each patient was given budesonide on two occasions:

1. first as CIR pellets (budesonide dose 18 mg) together with 4 mg of an oral ($^2H_8$)budesonide reference formulation after a heavy breakfast
2. then 2.5 months later, as an IV infusion of a mixture of budesonide (0.27 mg) and ($^2H_8$)budesonide (0.25 mg) after a light breakfast

Blood samples were taken for 72 hrs for budesonide pharmacokinetics.

Study 08- 3029

Healthy volunteers
This was an open study in six healthy male volunteers, randomized with a cross-over design. Each subject was given budesonide in two formulations simultaneously at each visit: as CIR capsules containing 4.5 mg budesonide pellets mixed with ^{111}In-labelled pellets and as a capsule containing 4.5 mg ($^2H_8$) budesonide mixed with lactose. Visit I (just before breakfast) and Visit II (immediately after breakfast) were at least 8 weeks apart. Blood samples were collected until 24 hr after drug administration for pharmacokinetic evaluation.

Study SD-051-0039

Patients with Crohn's Disease
This study was of an open, crossover and randomized design in 8 patients. Each patient received budesonide orally and ($^2H_8$) budesonide intravenously on two separate occasions: once in a fasting state and once after a heavy breakfast. Plasma concentrations of budesonide were determined for 12 hrs after the administration.

Budesonide CIR capsules in patients with Ileostomy [Study No. KN-005-94/51-3008]

Small-intestinal uptake of budesonide in CIR capsules and of micronized budesonide in plain capsules were compared in an open, randomized, cross-over design study 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 (see table below). This indicated that the release of budesonide from CIR formulation is delayed and/or prolonged compared to micronized budesonide in plain capsules.

Cumulative amounts (nmol) of d0-budesonide and d8-budesonide obtained during 24 h in effluent collected from eight ileostomy-operated subjects. On two separate occasions 3 mg (6842 nmol) d8-budesonide was administered as plain capsules together with 6 mg (13940 nmol) d0-budesonide as CIR (administration A) or as plain capsules (administration B), respectively.

	d0-budesonide		d8-budesonide	
Subject number	Administration A (CIR)	Administration B (Plain capsule)	Administration A (CIR)	Administration B (Plain capsule)
1	1142	158.4	114.4	78.60
2	317.9	227.8	59.17	102.2
3	2214	200.0	183.1	56.30
4	697.6	207.3	126.3	56.40
5	1929	120.0	< LOQ	18.50
6	616.3	78.70	< LOQ	< LOQ
7	612.1	282.0	62.07	98.20
8	1504	197.8	7.44	58.70
n	8	8	8	8
Mean	1129	184.0	69.05	58.61
Median	919.8	198.9	60.62	57.55
SD	690.0	63.64	67.42	35.70
CV%	61.1	34.6	97.6	60.9

< LOQ = Below limit of quantification, estimated as 0 (zero) in the calculations.

No differences in pharmacokinetic parameters, $AUC_{0-\infty}$, C_{max}, MRT, and T_{max}, were seen between the CIR capsule and the plain capsule.

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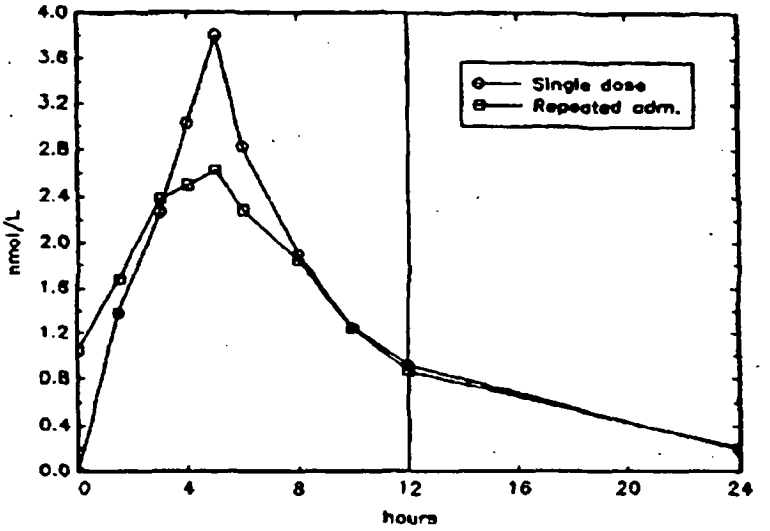
- **What are the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?**
- **Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?**

Single dose vs Repeated Dose

In study No. 08-3016, pharmacokinetics of budesonide CIR capsules was investigated in patients suffering from Crohn's disease after single dose and after repeated administration of 4.5 mg twice daily. The mean plasma budesonide for individual patients obtained after single and repeated dose administration are illustrated in the figure below:



The mean plasma concentration of budesonide after repeated administration was approximately the same at 0 and 12 hrs (1.05 vs 0.87 nmol/L, respectively), suggesting that steady state had been achieved. However, the mean plasma concentration 12 hrs after dose administration was the same after the single dose (0.91 nmol/L) as after repeated administration (0.87 nmol/L), indicating no accumulation. The table below shows the pharmacokinetic parameters after single and repeated dosing:

	single dose		repeated administration	
	mean	95% conf.lim.	mean	95 % conf.lim.
AUC (nmol·h/L)	28.5	22.5 - 36.0	21.1	17.3 - 25.7
T½ (h)	3.7	3.0 - 4.5	4.3	3.5 - 5.2
C_{max} (nmol/L)	4.1	3.4 - 5.0	3.2	2.7 - 3.8
C_{av} (nmol/L)			1.8	1.4 - 2.1
MRT (h)	8.0	6.8 - 9.2	9.2	8.0 - 10.4
		range		range
T_{max}(h)	4.7	1.6 - 8.0	4.4	1.5 - 8

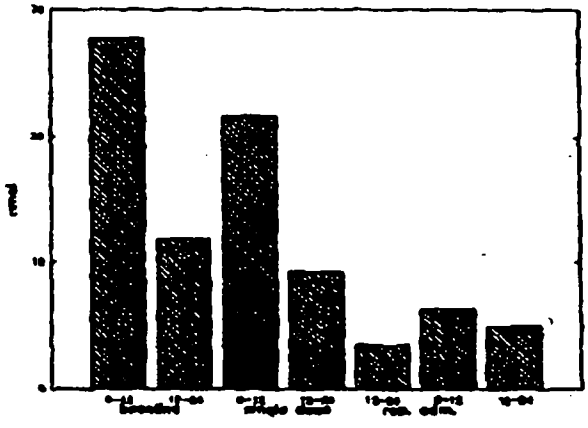
It was also investigated if there was a correlation between single and repeated dose pharmacokinetic parameters of CIR budesonide and safety/efficacy.

Suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function are often associated with glucocorticosterioids. In this study, safety data was collected as urinary cortisol suppression, which is a marker of HPA axis function.

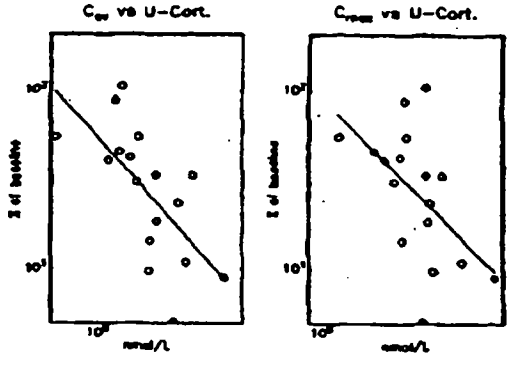
Efficacy was measured as the change from baseline in CDAI and van Hees index. The CDAI was calculated on the basis of signs and symptoms, clinical examination and the patient's hematocrit value. Signs and symptoms include the number of liquid or very soft stools per day, abdominal pain rating (none, mild, moderate and severe) and general well-being (generally well, slightly under par, poor, very poor and terrible). These signs and symptoms were recorded by the patient on a daily basis in the patients diary card.

The van Hees index was calculated on the basis of serum albumin, ESR, body weight related to length, abdominal mass, sex, temperature, stool consistency, bowel resection and extra-intestinal symptoms related to Crohn's disease.

Geometric means of cortisol excreted in urine are illustrated in the following figure



Cortisol levels excreted in the urine was higher during the day (0 – 12 hr) than during the night (12 – 24 hr) at baseline and during treatment. The mean cortisol levels excreted in the urine decreased to 27% of baseline during the night after repeated dosing for 8 weeks, but recovered partly (to 42% of baseline during the night) at the first day of the dose tapering stage. As shown in the following figure, high concentrations of plasma budesonide resulted in a larger suppression of cortisol excreted in the urine.



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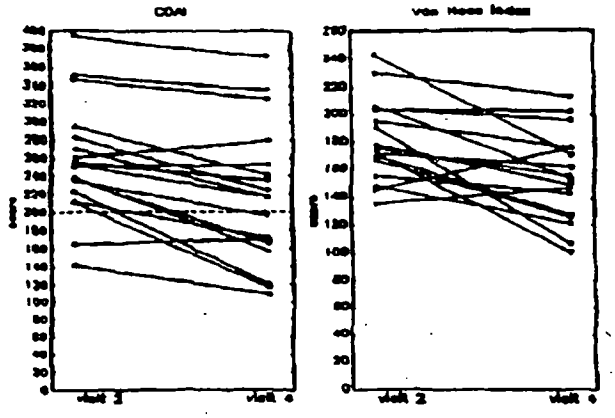
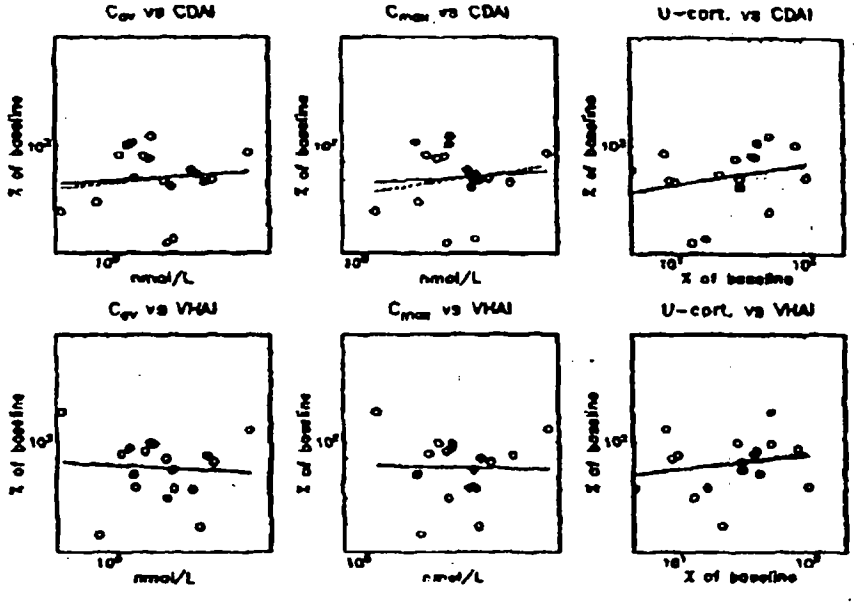
Following figure shows the individual changes in CDAI and van Hees index



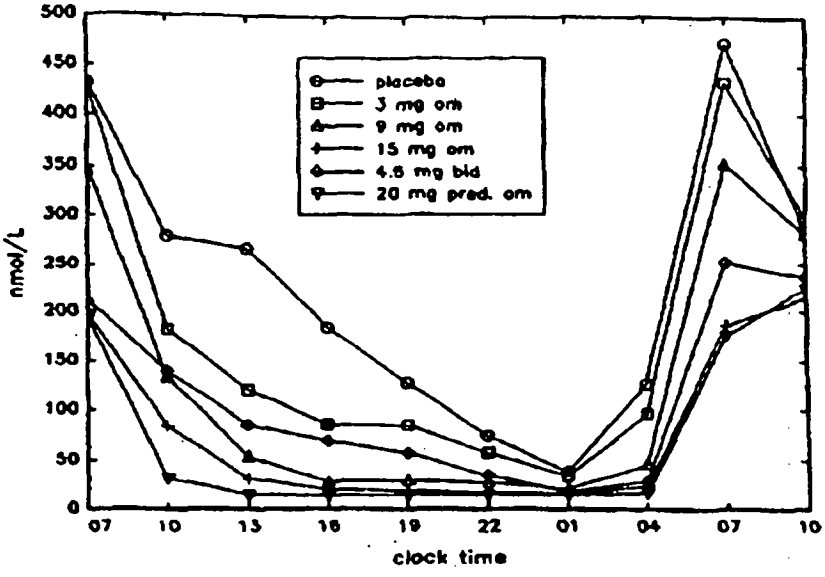
Mean CDAI index decreased by 44 units (from 270 – 226) and mean van Hees index decreased by 26 units (from 186 – 160). Pharmacokinetic parameters (C_{av} and C_{max}) and urine cortisol levels were plotted against effects expressed as change in CDAI and van Hees index, as shown in the figure below.



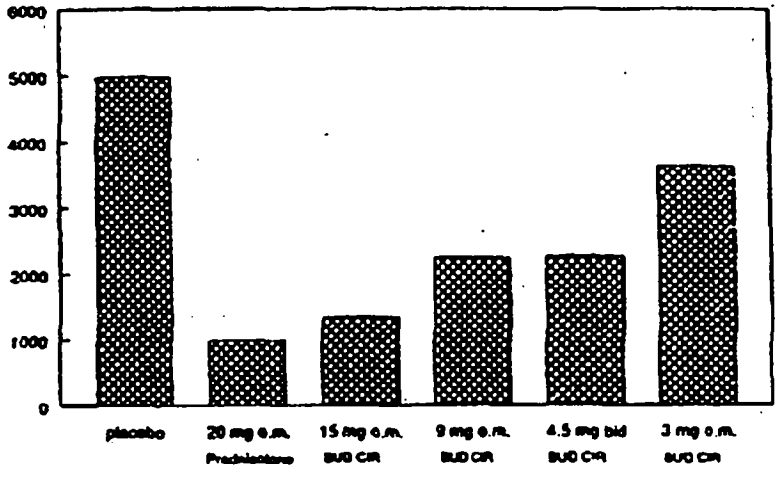
None of the regression lines have a clear slope. None of the coefficients of correlation were significantly different from zero. This data indicate that therapeutic action if observed is probably exerted locally in the bowel and not due to action on HPA-axis function mediated via systemically absorbed drug.

Budesonide CIR vs Prednisolone

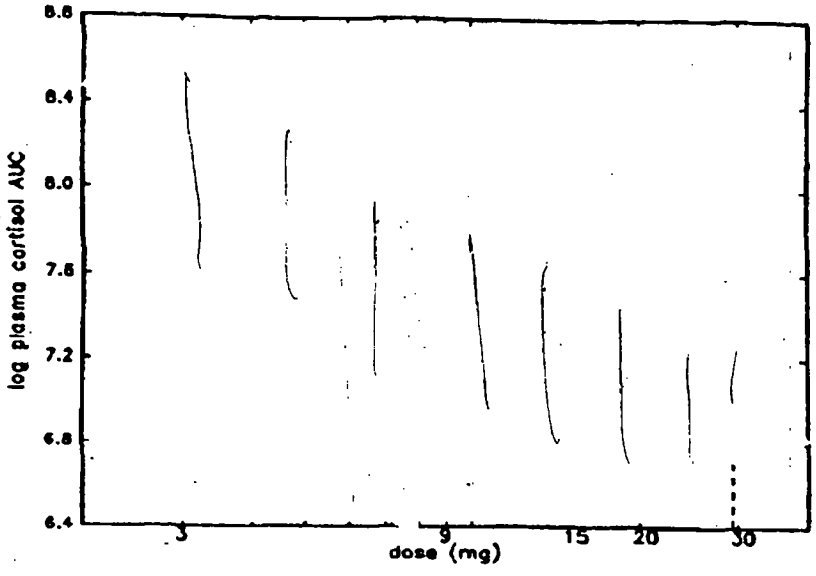
A double-blind, cross-over, randomized and placebo-controlled study was conducted in 24 healthy volunteers (12 males and 12 females) to compare the effect of budesonide CIR capsules on endogenous cortisol levels to that observed with prednisolone. $AUC_{0\text{-}24h}$ of plasma cortisol decreased with increasing doses of budesonide CIR. There is no difference between 9 mg budesonide CIR and b.i.d. 4.5 mg budesonide CIR. As shown in the following figure, prednisolone 20 mg suppressed plasma cortisol even more than 15 mg budesonide CIR. *[Although not approved for this indication, 40 mg Prednisolone is currently the standard regimen for the treatment of active mild to moderate Crohn's disease]*



The geometric mean of plasma cortisol $AUC_{0\text{-}24hr}$ (nmol.hr/L) are given in the following figure:



The amount of cortisol excreted in the urine was however found to be higher for 20 mg prednisolone than for 15 mg budesonide CIR. Assuming a log-linear dose response for plasma cortisol suppression, prednisolone is about 1.5 times as potent [20 mg prednisolone equivalent to 29 mg budesonide CIR] as budesonide CIR in its effect on plasma cortisol (see following figure). On the other hand, when log-linear dose response was plotted for urinary cortisol excretion it turned out that 20 mg prednisolone corresponds to 13 mg budesonide CIR (figure not shown).



Osteocalcin levels in serum or plasma, a sensitive index of bone turnover in many metabolic disorders of the bone was also measured. It was shown that decreased osteocalcin levels after prednisolone correlated with a reduction in bone density. In this study, 9 and 15 mg budesonide CIR and after 20 mg prednisolone, osteocalcin decreased significantly as compared to placebo. There were no differences in osteocalcin values between these treatments, however, b.i.d. 4.5 mg budesonide gave lower suppression of osteocalcin values than 9 mg budesonide CIR.

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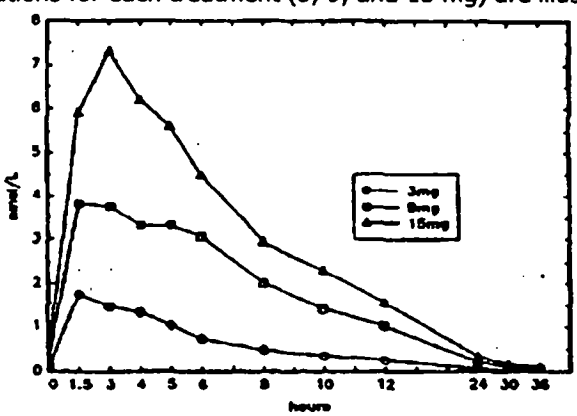
Dose Proportionality

An open, three-way crossover and randomized study [Study 08-3019] was conducted in 13 healthy volunteers (5 males and 8 females). Budesonide CIR capsules were given orally in three different dosage regimens: 3 mg, 9 mg and 15 mg for 5 days each and with at least 8 weeks between treatments. Blood samples were collected during day 5 of each treatment. Plasma concentrations of budesonide increased linearly with the dose within the investigated dose range of 3 – 15 mg. *Plasma cortisol levels or effect on amount of cortisol excreted in the urine was determined in this study.*

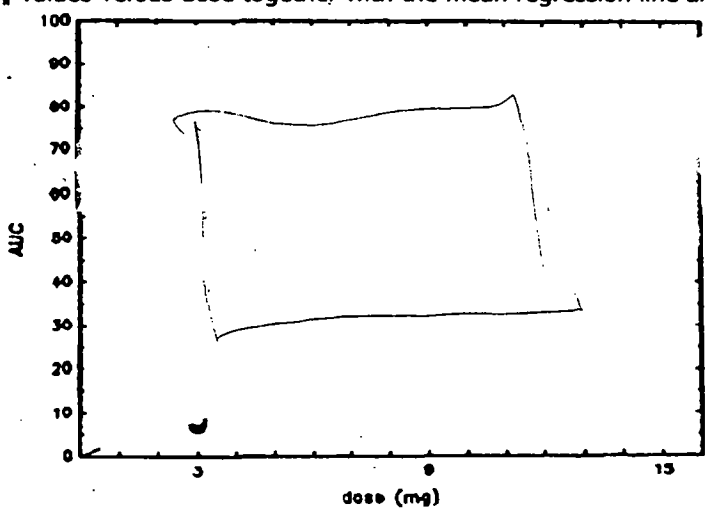
Pharmacokinetic results are summarized below:

Budesonide CIR dose, o.m.	C_{max} (nmol/L) (SD)	T_{max} (h) (range)	MRT (h) (SD)	AUC_{0-12h} nmol·h/L (SD)
3 mg	1.9 (0.66)	2.3	12.3 (4.0)	11.5 (3.5)
3 x 3 mg	5.3 (1.8)	2.7	7.8 (1.8)	37.0 (14.6)
3 x 5 mg	8.0 (2.3)	3.1	8.0 (1.5)	60.2 (16.5)

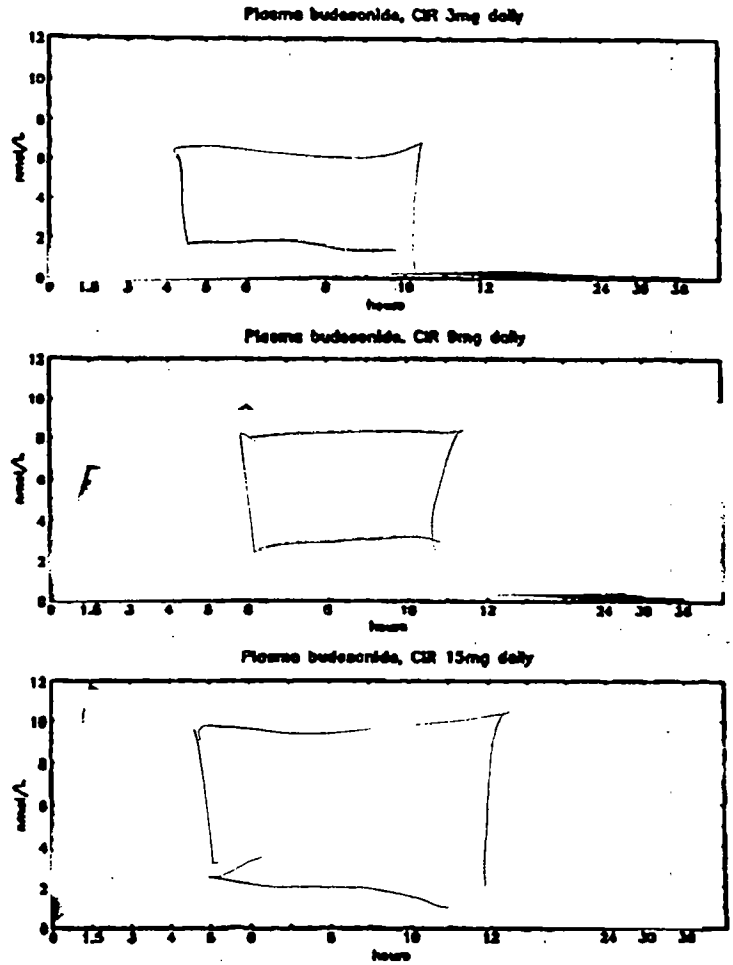
Mean plasma concentrations for each treatment (3, 9, and 15 mg) are illustrated in the following figure:



Individual AUC_{0-24hr} values versus dose together with the mean regression line are illustrated in the figure below:



Individual plasma budesonide concentrations are shown in the following figure. Based on these profiles, it appears in fewer subjects and only at higher doses this formulation exhibited delayed release characteristics whereas in others it behaved like an immediate release formulation. Individual T_{max} values varied between 1.5 – 6.0 hrs (Appendix III).



- **What are the intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) that influence exposure or response, what is their impact on exposure and/or response?**
- **Based upon what is known about exposure response relationships and their variability is dose adjustment recommended depending on any factor/s?**

Hepatic Insufficiency

Budesonide is normally cleared 85-90% by hepatic biotransformation. A compromised liver function could therefore influence its kinetic and hence dynamic properties. This was investigated in a study (10-3002) of 16 subjects where 4 subjects with mild liver cirrhosis and 4 subjects with moderate liver cirrhosis (Child Pugh classification A & B, respectively) were matched with 8 healthy controls with regard to age and sex.

Hepatic status in Cirrhotic patients

- Reduced blood flow through the liver and abnormal plasma protein pattern compared with the healthy controls
- Lower demethylation of dimethylaminoantipyrine (DMA) as assessed by DMA-breath test
- Increased 24 hr concentration of theophylline after oral administration
- Increased (50%) urinary excretion 6β-hydroxycortisol

This study included three sessions:

1. Baseline test of plasma and urinary cortisol
2. Budesonide given as a single intravenous infusion of 0.5 mg
3. Budesonide given as an oral dose of 4 mg

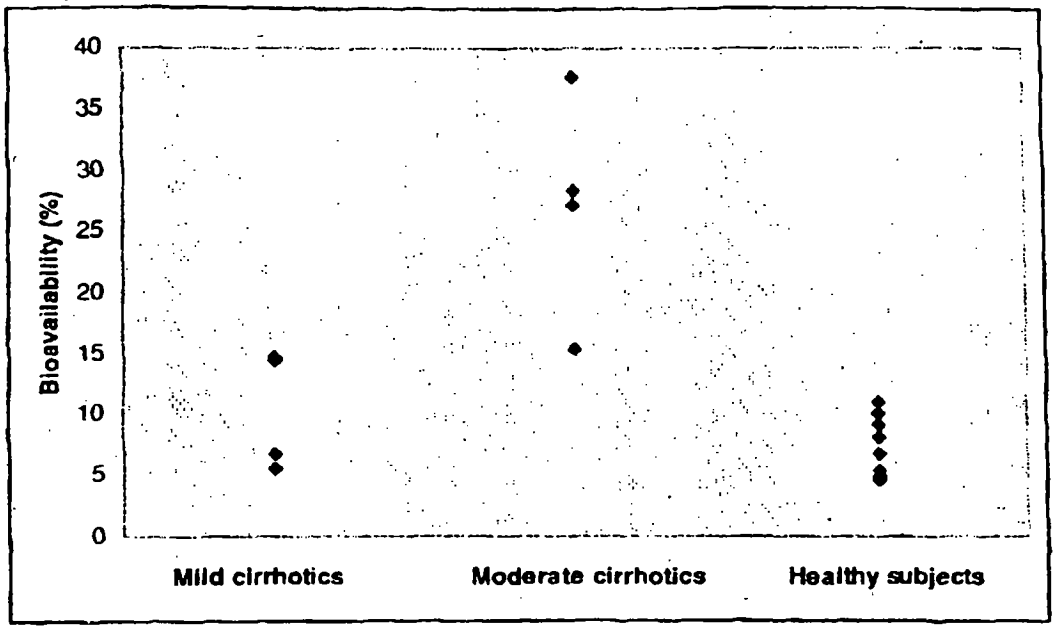
Results

In the study report, pharmacokinetic comparison was made between cirrhotics and healthy controls:

Parameters	Cirrhotics	Healthy controls
$T_{1/2}$ (hr)	4.6 ± 1.0	3.6 ± 0.5
V_{ss} (L)	167 ± 56	163 ± 41
CL (ml/min)	767 ± 214	908 ± 177
F (%)	18.6 ± 11.2	7.4 ± 2.4
C_{max} (nmol/L)	5.1 ± 3.4	1.7 ± 0.3
T_{max} (hr)	3.8 ± 1.7	3.6 ± 1.8

In the summary section, cirrhotics were classified into mild and moderate subgroups and the individual bioavailabilities were compared to healthy controls as shown in the following figure:

Individual Bioavailability-Values of Budesonide After Administration of Single Doses of Plain Capsules 4 mg to Subjects with Liver Impairment



On average, systemic availability of orally administered budesonide was 2.5-fold higher in patients with liver cirrhosis compared with healthy controls. Patients with mild liver disease were minimally affected, whereas patients with severe liver dysfunction were not studied. Under these circumstances it is recommended (*per Guidance for Industry*) that findings in the moderate category will be applied to the mild category and dosing in the severe category would be generally contraindicated. Thus, a 2.5 –fold reduction in dose is recommended in patients with mild and moderate liver cirrhosis.

Renal Insufficiency

Intact budesonide is not renally excreted. Only metabolites with negligible corticosteroid activity are excreted in the urine to a large extent. Thus, pharmacokinetics of budesonide was not studied in patients with renal impairment.

Sex

An open, three-way crossover and randomized study [Study 08-3019] was conducted in 13 healthy volunteers (5 males and 8 females). Budesonide CIR capsules were given orally in three different dosage regimens: 3 mg, 9 mg and 15 mg for 5 days each and with at least 8 weeks between treatments. No difference in pharmacokinetics of budesonide was observed between men and women.

In another open design study [Study 08-0204] conducted in six patients with Crohn's Disease (3 men and 3 women), each patient was given 18 mg dose of budesonide CIR pellets. Again no difference in pharmacokinetics of budesonide was observed between men and women.

Elderly

No specific study was conducted in elderly subjects, aged 65 years or older. Two healthy subject, 74 and 78 years of age, participated as controls in the study with liver cirrhotic patients. These two elderly subjects had similar pharmacokinetics as other six healthy controls in that study

Pediatric

Pharmacokinetic data from 4 children between 9 – 13 years were compared with 4 adults in Study 08-CR-3044/I. AUC and systemic bioavailability were 30% and 45% lower, respectively, in children with active Crohn' disease.

According to the Medical Officer reviewer for this NDA, 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. It was also recommended that partial waiver request for pediatric studies in patients below 6 years of age be granted and that well controlled studies should be done in patients with Crohn's disease patients 6 to 17 years of age to evaluate the safety and efficacy of ENTOCORT as a phase 4 commitment.

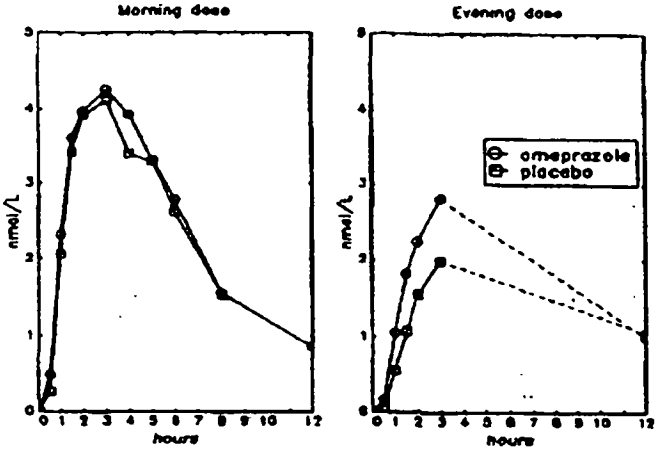
- **What are the extrinsic factors (drugs, herbals, diet, smoking, alcohol use) that influence exposure or response?**
- **If dosage regimen adjustments across groups are based upon factors other than the exposure-response relationships, please indicate so.**

Drug-Drug Interaction

Omeprazole

Omeprazole inhibits gastric acid secretion via a selective and non-competitive antagonism of the gastric proton pump (H^+, K^+-ATPase) in the secretory membrane of the parietal cell. Since budesonide CIR pellets are pH-dependent, the effect of 20 mg omeprazole on the pharmacokinetics and systemic effects of budesonide CIR capsules was studied in a double-blind, randomized, cross-over and placebo-controlled study in 11 healthy volunteers (6 males and 5 females). Budesonide CIR capsules 9 mg were given at two visits, with at least 12 weeks between treatments. The subjects received omeprazole during one treatment period and placebo during the other period, once daily in the morning for six days. On the 5th day, budesonide CIR capsules 9 mg were given in the morning with 20 mg omeprazole or placebo, and the following day another budesonide CIR capsule was given in the evening.

Mean plasma concentrations of budesonide after the morning and the evening doses are shown in the figure below (the dashed lines show that no samples were taken between 3 and 12 hrs after administration):



Omeprazole did not effect budesonide plasma concentration after the morning dose. However, after the evening dose for the first 3 hrs, the mean concentration of budesonide were larger with omeprazole than with placebo. At 12 hrs, the mean plasma concentrations were similar for both placebo and omeprazole. Budesonide pharmacokinetic results are summarized below:

Budesonide pharmacokinetics: Morning dose				
	omeprazole period		placebo period	
	geometric mean	95% conf. lim.	geometric mean	95% conf. lim.
AUC_{0-12h} (nmol x h/L)	29.1	23.6-36.0	29.4	23.1-36.8
C_{max} (nmol/L)	4.17	3.32-5.23	4.19	3.34-5.27
	arithmetic mean	95% conf. lim.	arithmetic mean	95% conf. lim.
MRT (h)	7.5	6.7-8.4	7.9	7.0-8.7
T_{max} (h)	3.2	(range 1.0-6.0)	2.9	(range 1.0-5.0)

Budesonide pharmacokinetics: Evening dose				
	omeprazole period		placebo period	
	geometric mean	95% conf. lim.	geometric mean	95% conf. lim.
$AUC_{0,1h}$ (nmol x h/L)	3.4*	1.5-7.7	2.6*	1.2-5.9
$C_{max\ obs}$ (nmol/L)	2.59*	1.34-5.00	1.84*	0.95-3.56
	arithmetic mean	range	arithmetic mean	range
T_{max} (h)	2.6*	1.5-3	2.8*	2.0-3.0

Urine cortisol excretion was significantly lower after the morning and evening budesonide doses compared to baseline, however, no statistically significant difference between the treatments were observed.

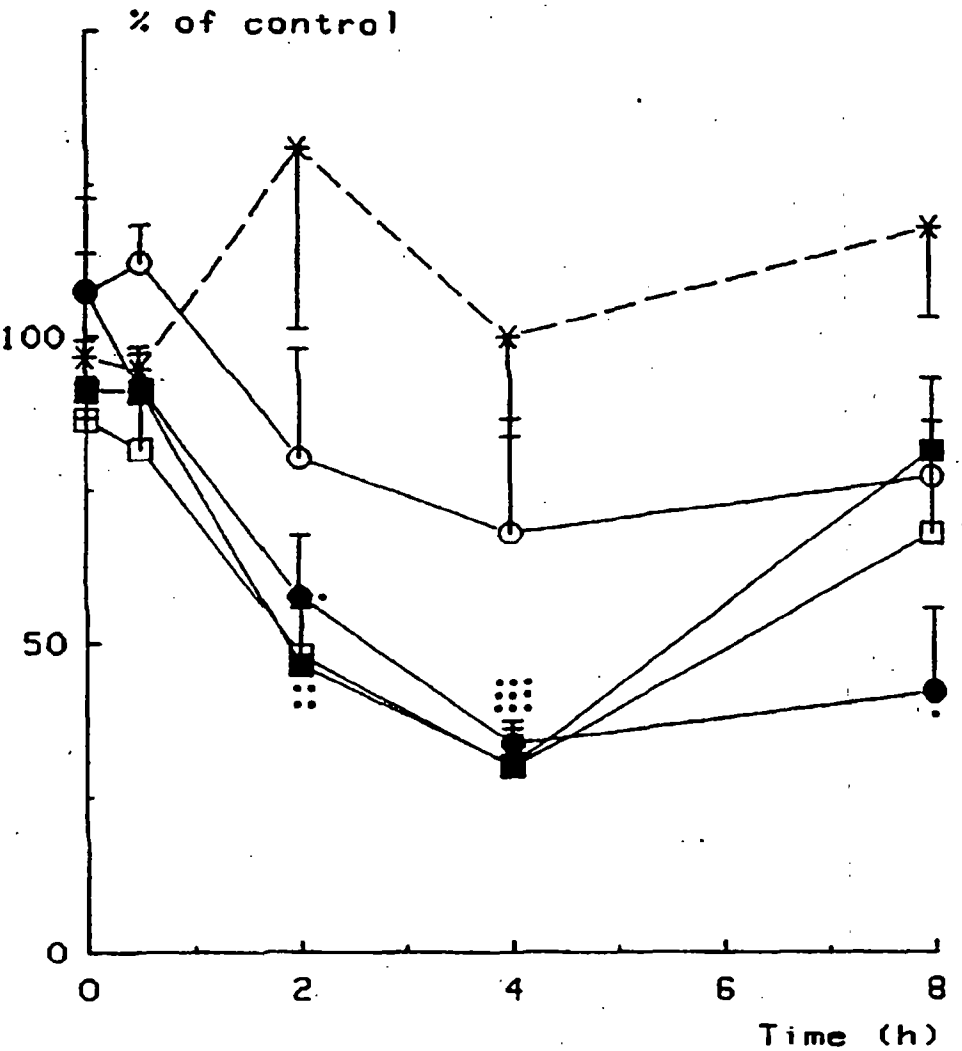
Cimetidine

Pharmacokinetics and pharmacodynamics of budesonide were examine in 6 healthy subjects after 0.5 mg IV and 4 mg oral administration of plain micronized budesonide. The drug was given with and without concomitant oral intake of cimetidine (1 g daily for three days). Following table summarizes the pharmacokinetic results:

Parameters	Without Cimetidine	With Cimetidine
Intravenous		
$T_{1/2}$ (hr)	2.0 ± 0.5	1.9 ± 0.2
V_{ss} (L/kg)	1.5 ± 0.6	1.4 ± 0.5
CL (L/min)	1.0 ± 0.2	0.9 ± 0.2
Oral		
C_{max} (nmol/L)	3.3 ± 1.5	5.1 ± 1.6
T_{max} (hr)	1.5 ± 0.8	1.5 ± 0.8
Systemic availability (% of dose)	10 ± 3	12 ± 3

Although pharmacokinetics of IV budesonide was not affected by cimetidine, C_{max} and systemic availability was slightly higher after oral budesonide during cimetidine treatment. This indicated that the rate of absorption of budesonide was slightly affected by cimetidine.

As shown in the figure below, after oral administration of budesonide cortisol suppression was significant only when taken with cimetidine.

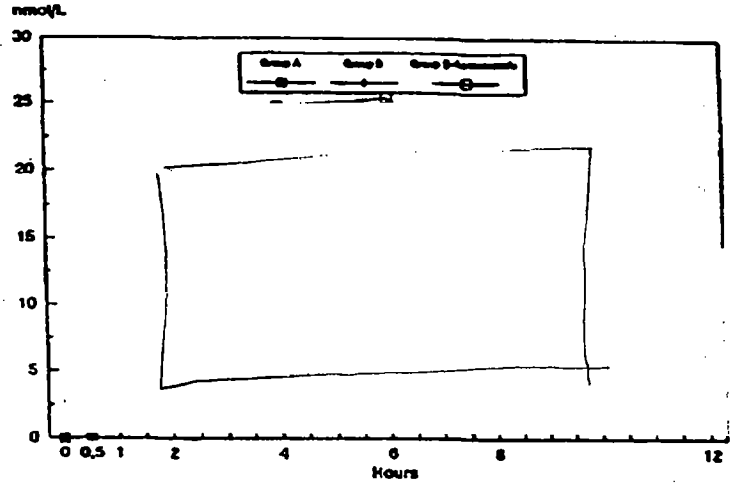


Plasma cortisol concentrations (mean ± sem) after 0.5 mg intravenous and 4 mg oral budesonide, with and without concomitant treatment with cimetidine. In a separate experiment, plasma cortisol concentrations were studied after cimetidine alone. Values are given at scheduled sampling times. Significant deviations from control values are denoted by asterisks (*=p<0.05, **=p<0.005, and ***=p<0.001). All doses were given within 50 min of 8 a.m.

■ ; intravenous budesonide, with cimetidine
□ ; intravenous budesonide, without cimetidine
● ; oral budesonide, with cimetidine
o ; oral budesonide, without cimetidine
✳ ; cimetidine alone.

Ketoconazole

In vitro studies have demonstrated CYP3A mediated metabolism of budesonide to two major metabolites, 16α-hydroxyprednisolone and 6β-hydroxybudesonide. Thus an open, cross-over study was designed to investigate pharmacokinetic properties of budesonide with or without ketoconazole, a known CYP3A inhibitor, in ten healthy subjects in two groups. Group A consisted of 4 subjects who had shown a high degree of cortisol suppression with budesonide and Group B included 6 subjects who had shown low degree of cortisol suppression. A single oral dose of 10 mg budesonide was given which was followed by a wash-out period of one week. Thereafter, subjects in group B were given 100 mg ketoconazole b.i.d. orally for 3 consecutive days. Single oral dose of 10 mg budesonide was given with the last ketoconazole dose. Plasma concentration time curve for budesonide in subjects from group A & B including the period with ketoconazole treatment are shown in the figure below:



Pharmacokinetic parameters are summarized in the table below:

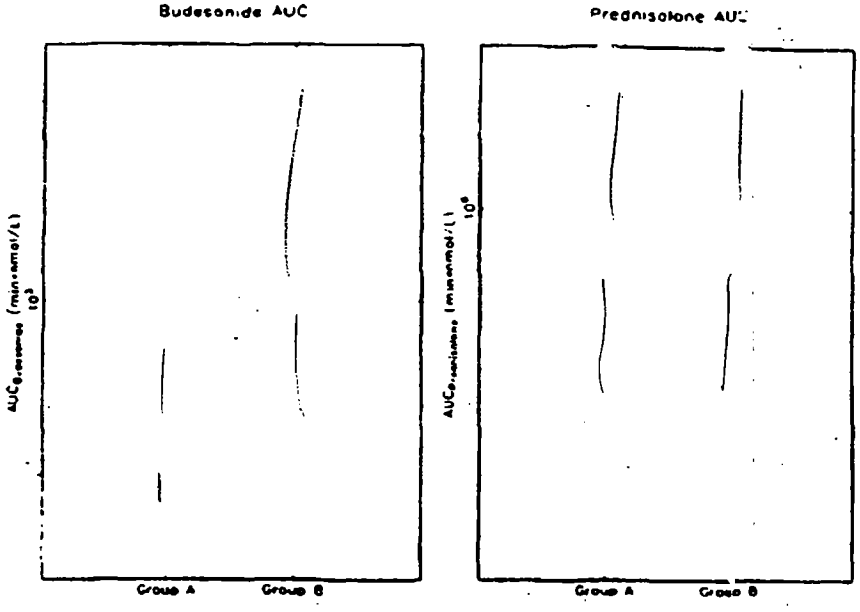
	AUC_{0-12}	C_{max}	t_{max}	$t_{½}$	MRT	
Group A						
Mean	52.3	6.1	3.5	4.7	8.0	
Min						
Max						
Group B						
Mean	31.6	5.2	4.2	3.5	7.3	
Min						
Max						
Group B + Ketoconazole						
Mean	238.2	34.9	5.0	3.1	7.6	779
Min						
Max						

The plasma concentrations of budesonide increased substantially when the subjects in group B were pretreated with ketoconazole. Almost eight-fold increase in AUC was observed in these subjects. In group A, the decrease in average concentration of plasma cortisol was 82% after administration of budesonide. The corresponding decrease in group B was 62%. When both budesonide and ketoconazole were given, the plasma cortisol levels were below the limit of quantitation. The decrease in total amount of cortisol excreted in the urine during 24 hrs was nearly the same in group A and group B (59% and 56%, respectively). The combined administration of budesonide and ketoconazole gave cortisol levels below the limit of quantitation.

The influence of the dosing time of ketoconazole on the pharmacokinetics of budesonide was also evaluated in an open, randomized, cross-over study. When budesonide and ketoconazole were given simultaneously in the morning, plasma concentrations of budesonide over 24 hrs, calculated as $AUC_{0\text{-}24hr}$, were increased ~7-fold, compared to baseline without ketoconazole. A smaller increase, 4-fold, was seen when budesonide and ketoconazole were administered with a time difference of 12 hrs.

Oral contraceptive (Desolett®)

The effect of oral contraceptive on the plasma level of budesonide and prednisolone was investigated in a single-blind, randomized, and placebo-controlled cross-over study in two parallel groups. Group A included 20 subjects using Desolett, containing desogestrel 0.15 mg and ethinylestradiol 30 µg and Group B included 20 subjects without oral contraceptive. Standard pharmacokinetic parameters were evaluated after 7 days treatment with oral dose of 4.5 mg budesonide, 20 mg prednisolone, or placebo. AUC for budesonide and prednisolone concentrations in oral contraceptive users are plotted in the figure below. The solid symbols indicate group geometric means.



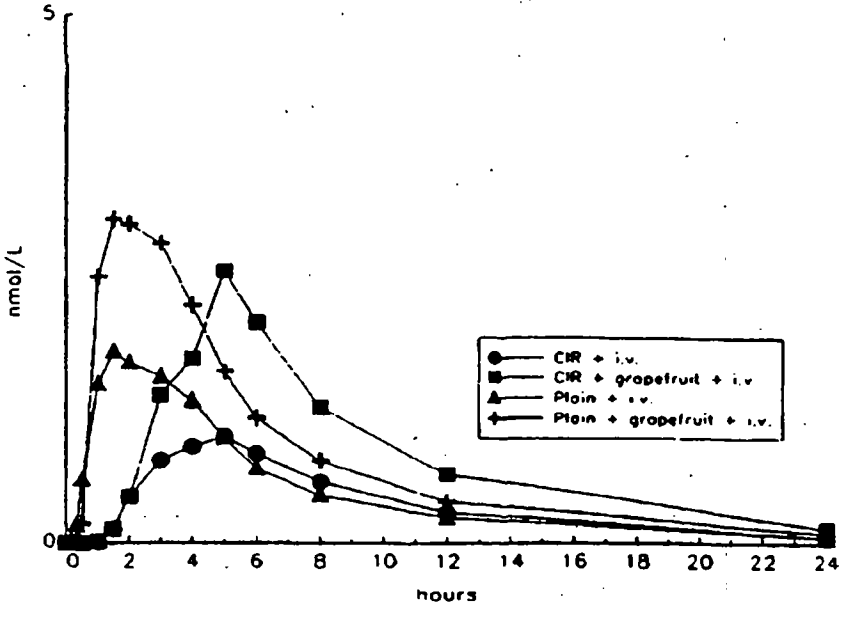
AUC of budesonide in Group A was estimated to be 22% greater than for Group B, whereas AUC for prednisolone was approximately 131% greater for women on contraceptives. Plasma cortisol was suppressed by 82% and 28% in Group B (without contraceptive) after administration of prednisolone and budesonide, respectively. In Group A (contraceptive users) the plasma cortisol suppression was 90% and 20%, respectively.

Diet (Grapefruit juice)

Inhibition of first-pass metabolism of budesonide caused by grapefruit juice was evaluated in an open, randomized cross-over study.

- In treatment period I, a single oral dose of 3 mg budesonide CIR was given at 8 AM.
- In treatment period II, 200 ml grapefruit juice was given 3 times a day for 4 days. On the 4th day, grapefruit juice was given at the same time as budesonide CIR.
- In treatment period III, budesonide (3 mg) in a plain capsule was given as a single oral dose at 8 AM.
- In treatment period IV, 200 ml grapefruit juice was given 3 times a day for 4 days. On the 4th day, grapefruit juice was given at the same time as plain budesonide.

Between each treatment period there were washout periods of at least one week. In all treatments, an IV dose of 0.2 mg deuterium-labeled budesonide was given at the same time as budesonide. Mean plasma concentrations of budesonide are shown in the figure below:



There was a clear increase in plasma concentrations after intake of grapefruit juice, both for CIR capsules and plain capsules. Intake of grapefruit juice resulted in about 2-fold increase of the bioavailability of budesonide taken as CIR or plain capsules. There was no significant effect of grapefruit juice intake on $T_{1/2}$, clearance, or V_d. MRT was significantly increased after intake of grapefruit juice. The mean increase was 0.47 hrs. V_{ss} was also significantly increased after intake of grapefruit juice. The mean increase was 15%.

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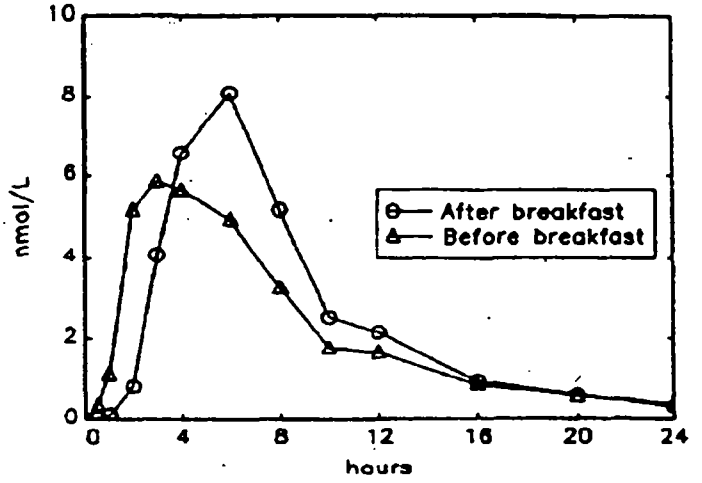
Food Effect

An open, cross-over, randomized study (Study SD-051-0039) was conducted in eight patients with Crohn's disease to compare the systemic bioavailability of budesonide in fasting state and after a heavy breakfast after an oral dose of 9 mg budesonide CIR. Heavy breakfast meal selected was high in calories and fat as recommended by FDA. Although extent of oral bioavailability and C_{max} of budesonide was not effected, absorption was delayed (T_{max} and MAT) after heavy breakfast.

PK Parameter	Fasting	Non-fasting	Mean diff.	95% conf. limits		P-value
AUC (nmol/Lxh)	31.2	30.7	0.45	-7.86	8.75	0.8996
F_{syst} (%)	11.65	15.11	-3.46	-9.37	2.45	0.2017
MAT (h)	4.49	6.83	-2.34	-3.34	-1.34	0.0012
C_{max} (nmol/L)	4.98	4.51	0.47	-1.18	2.12	0.5095
T_{max} (h)	3.75	6.25	-2.50	-3.89	-1.10	0.0045

Another open label study was conducted in eight healthy volunteers to study the influence of heavy breakfast on the pharmacokinetics of budesonide after an oral dose of 18 mg budesonide CIR. T_{max} was delayed and C_{max} was increased, but systemic (F%) bioavailability was not affected by concomitant intake of high fat breakfast. The mean plasma concentrations of budesonide are illustrated in the figure below:



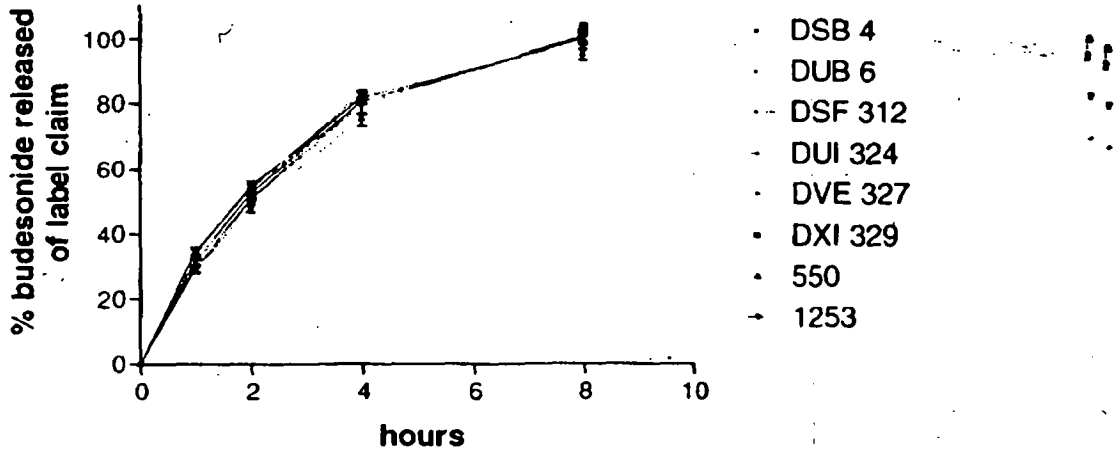
Pharmacokinetic parameters following administration in fasting state and after a heavy breakfast

	Administration in a fasting state			Administration after a heavy breakfast		
Parameter	Geometric mean	95 % conf.limits	Variance	mean	95 % conf.limits	Variance
C_{max} (nmol/L)	5.8	3.8 - 9.0	56 (CV%)	9.1	6.9 - 11.9	33 (CV%)
F (%)	9.1	6.7 - 12.3	37 (CV%)	11.5	9.6 - 13.9	23 (CV%)
Parameter	mean	95 % conf.limits	Variance	mean	95 % conf.limits	Variance
MAT (h)	5.8	5.1 - 6.5	0.9 (SD)	6.4	5.4 - 7.4	1.2 (SD)
AUC (nmolxh/L)	54.1			62.4		
MRT (h)	8.0			8.6		
T_{max}	3.1			5.4		

- **Is the *in vitro* release method and proposed specifications adequate to describe the *in vitro* release profile of the product?**

The *in vitro* dissolution of budesonide from pellets used was tested in simulated gastric (pH 1.2) and intestinal (pH 7.5) fluids at 37°C using a flow through cell methodology [Wennergren et al., Int. J. Pharm; 1989; 53: 35 – 41]. According to the sponsor [*in vivo* biopharmaceutics section in summary], all batches used in the clinical and clinical pharmacology documentation of ENTOCORT capsules have involved the same formulation, consisting of microgranules with sustained release properties. The sponsor further suggested that the release properties *in vitro* of all batches were essentially similar and small difference noted is not expected to affect the pharmacokinetic results and the clinical outcome. A comparison of drug release profiles of representative batches used for bio-batches, clinical studies and stability studies to batches made at production scale are presented in a table (see Appendix V) and the figure below:

Drug Release Profiles at pH 7.5 for Representative Batches of Entocort Capsules (average and range, N=6)



Dissolution Specifications for Entocort Capsules 3 mg

Drug release at pH 1.2:	In USP apparatus 4 with 12 mm flow-through cells at 8 ml/min and 37°C Performed on one composite sample consisting of the contents from 8 capsules. of labeled content after 2 hrs.
Drug release at pH 7.5:	In USP apparatus 4 with 12 mm flow-through cells at 8 ml/min and 37°C After 1 hr – % of labeled content After 2 hr – % of labeled content After 4 hr – % of labeled content After 8 hr T % of the labeled content

Based on the data presented on biobatch at release and drug release profiles in stability studies, the sponsor's proposed specification of NLT 88% after 8 hr seems reasonable. However, after 4 hr the specification should be changed to ; after 2 hr to ; and after 1 hr to The specification of drug release at pH 1.2 of after 2 hrs seems appropriate.

Appendix I

Study 08-3020: **Pharmacokinetic comparison between budesonide and ($^2H_8$) budesonide after oral dosing in man.**

Purpose of this study was to find out if ($^2H_8$) budesonide can be used as a simultaneously given reference standard in bioavailability studies. This was done by comparing the pharmacokinetics of epimers (22R) and (22S) of budesonide and ($^2H_8$)budesonide after oral dosing.

Study Design:

This was an open study in six healthy volunteers (3 men and 3 women).

Budesonide and ($^2H_8$) budesonide (4.14 + 3.98 mg) were given together as a single oral dose in the morning after an overnight fasting and just before a standardized breakfast.

Plasma samples for pharmacokinetic evaluation were taken for 10 hrs.

Results and Discussion:

The plasma concentration ($^2H_8$) budesonide was always higher than that of budesonide.

The AUCs for epimers (22S) and (22R) of budesonide were 644 ± 215 and 46 ± 35 nmol.h/L, respectively.

The AUCs for epimers (22S) and (22R) of ($^2H_8$) budesonide were 830 ± 357 and 70 ± 48 nmol.h/L, respectively.

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Appendix II

Study 08-3015

Pharmacokinetic parameters of absorption for budesonide CIR

No.	AUC (nmol*h/L)	F (%)	C_{max} (nmol/L)	T_{max} (min)	MAT (h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
N	12	12	12	12	12
MEAN	30.77	9.64	4.880	192.6	4.136
STD	14.41	3.63	1.890	118.2	1.516
MIN	14.5	6.1	2.30	30	1.96
MEDIAN	24.8	8.6	4.12	180	3.75
MAX	58.4	16.7	8.69	360	6.92

Appendix II contd.

Pharmacokinetic parameters of absorption for plain budesonide

No	AUC (nmol*h/L)	F (%)	C_{max} (nmol/L)	T_{max} (min)	MAT (h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
N	12	12	12	12	12
MEAN	31.43	9.71	5.108	240.0	4.197
STD	17.05	4.01	2.600	44.3	1.287
MIN	16.0	5.4	2.09	180	2.26
MEDIAN	24.3	8.5	4.28	240	4.24
MAX	67.7	17.1	9.52	360	6.04

subject	(15mg) k_{el}	(15mg) $T_{\frac{1}{2}}$ (h)	3mg AUC (nmol·h/L)	3mg MRT (h)	3mg C_{max} (nmol/L)	3mg T_{max} (h)	3mg AUC/dose (nmol·h/L/mg)	9mg AUC (nmol·h/L)	9mg MRT (h)	9mg C_{max} (nmol/L)	9mg T_{max} (h)	9mg AUC/dose (nmol·h/L/mg)	15mg AUC (nmol·h/L)	15mg MRT (h)	15mg C_{max} (nmol/L)	15mg T_{max} (h)	15mg AUC/dose (nmol·h/L/mg)
1																	
2																	
3																	
5																	
6																	
7																	
8																	
10																	
11																	
12																	
13																	
N	12	12	12	12	12	12	12	13	13	12	12	12	12	12	12	12	12
MEAN	0.120	6.08	11.467	12.340	1.937	2.293	3.822	31.025	7.760	5.230	2.714	4.114	60.186	7.985	7.983	3.002	4.012
STD	0.024	1.86	3.482	3.935	0.635	1.114	1.161	14.610	1.782	1.766	1.747	1.624	16.509	1.506	2.767	1.390	1.101
MIN	0.06	4.44	7.25	8.14	1.29	1.50	2.42	24.79	6.11	3.00	1.50	2.75	34.14	6.22	6.16	1.50	2.28
MEDIAN	0.11	5.60	10.99	11.27	1.76	1.52	3.66	27.38	6.93	3.33	1.53	3.60	55.41	7.90	8.00	3.00	3.69
MAX	0.16	11.81	16.84	22.68	3.33	5.00	5.61	77.38	10.67	9.02	8.00	8.50	89.89	10.67	11.88	8.00	5.97

Appendix IV

Report #	# of Subjects M/F	Dose (mg)	Formulation / before or after meal	AUC (nmol.hr/ml)	C_{max} (nmol/L)	T_{max} (hr)
850-CR-3015	6/6	9	Plain capsule / just before meal	31.4	5.1	4.0
	6/6	9	CIR capsule / just before meal	30.8	4.9	3.2
850-CR-3029	6/0	4.5 + 4.5	Plain capsule with lactose + CIR / just before meal	18.0 (plain) 18.0 (CIR)	3.3 (plain) 2.6 (CIR)	1.8 (plain) 4.5 (CIR)
	6/0	4.5 + 4.5	Plain capsule with lactose + CIR / just after meal	18.5 (plain) 16.9 (CIR)	2.8 (plain) 2.7 (CIR)	2.9 (plain) 5.2 (CIR)
850-CR-7018/B	3/3	4 + 18	Plain capsule with lactose + CIR / just after meal	21.3 (plain) 127.9 (CIR)	2.7 (plain) 17.9 (CIR)	3.5 (plain) 8.0 (CIR)
850-CR-7018/A2	4/0	18	CIR capsules / fasting	41.9	5.5	2.5
	4/0	18	CIR capsules / just after meal	53.5	7.8	5.0
08-CR-3019	5/8	3	CIR capsules / just before meal	11.5	1.9	2.3
		9	CIR capsules / just before meal	37.0	5.3	2.7
		15	CIR capsules / just before meal	60.2	8.0	3.1
08-CR-3016	10/8	4.5 bid	CIR capsules / just before meal	30.0	4.2	5.8
51-CR-3008	7/1	6 + 6	Plain capsule with lactose + CIR	26.2	4.40	3.4
	7/1	12	Plain capsule with lactose	25.9	4.1	2.3
850-CR-7018/1	1/1	9	CIR capsules / fasting		3.0	13.0

Appendix V

Drug Release Results for Representative Batches of Entocort Capsules

Capsule Batch No.	Mfg. site	Date of Mfg. (month/ year)	Use of batch	Granule Batch No.	Scale (kg)	Process drying conditions	Drug release (average and range, N=6, % of labeled content)				
							pH 1.2	pH 7.5			
							2 hours	1 hour	2 hours	4 hours	8 hours
DSB 4	AZ R&D Lund	2/1992	Clinical pharmacological	DSB 10		Bed temperature 70°C, 30 min	1	34 (33-36)	54 (53-55)	82 (80-84)	100 (98-103)
DUB 6	AZ R&D Lund	2/1994	Clinical pharmacological	DTL 30			1	30 (30-30)	51 (50-51)	81 (80-82)	101 (99-103)
DSF 312	AZ R&D Lund	8/1992	Clinical pharmacological, Clinical	DSE 11			1	34 (33-34)	54 (54-55)	83 (82-84)	103 (101-105)
DUI 324	AZ R&D Lund	9/1994	Clinical pharmacological, Clinical	DUI 40			2	32 (32-33)	53 (52-53)	81 (80-81)	100 (98-102)
DVE 327	AZ TPS Södertälje [a]	5/1995	Clinical	104		Inlet temperature 85°C, 45 min	1	31 (30-32)	53 (51-54)	82 (80-83)	101 (98-102)
DXI 329	AZ TPS Södertälje [a]	9/1996	Clinical	1009			1	35 (34-36)	55 (54-56)	82 (80-83)	101 (99-101)
XC 550	AZ TPS Södertälje	6/1996	NDA stability	1001			1	29 (28-30)	49 (47-50)	76 (73-77)	95 (94-97)
BB 1253	AZ TPS Södertälje	3/2000	NDA Stability	1253		Bed temperature 82°C, 30 min	1	29 (28-30)	51 (49-52)	80 (77-82)	101 (98-104)

[a] Capsules filled at AZ R&D Lund

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

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21 pages

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-324	Brand Name	Entocort
OCPB Division (I, II, III)	II	Generic Name	Budesonide
Medical Division	DGICDP	Drug Class	Glucocorticosteroid
OCPB Reviewer	Sandip Roy	Indication(s)	Treatment of mild to moderate active Crohn's disease involving ileum
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Capsules
		Dosing Regimen	9 mg QD
Date of Submission	1/24/01	Route of Administration	Oral
Estimated Due Date of OCPB Review	6/11/01	Sponsor	Astra Zeneca
PDUFA Due Date	7/24/01	Priority Classification	P
Division Due Date	6/25/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:	X	5		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X			
multiple dose:	X	1		
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:		2		
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:		6		
In-vivo effects of primary drug:		1		
In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:	X			
pediatrics:	X	1		
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		

PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	1		
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:	X	2		
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				Requested Deferral
Literature References				
Total Number of Studies	[redacted]	21		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	(1) Is the delayed + extended release characteristics of the dosage form adequately characterized? (2) Is there a concentration-response relationship for the systemic steroid effects? (3) Is the in vitro release method and proposed specifications adequate to describe the in vitro release profile of the product?	
Other comments or information not included above		
Primary reviewer Signature and Date	Filing only- Suresh Doddapaneni, 2/26/01	
Secondary reviewer Signature and Date	Suresh Doddapaneni, 2/26/01	

CC: NDA 21-324, HFD-850(Electronic Entry or Lee), HFD-180(McNeil), HFD-870(Doddapaneni, Malinowski, Hunt), CDR (B. Murphy)

/s/

Suresh Doddapaneni
2/26/01 08:13:15 AM
BIOPHARMACEUTICS

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