CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-324

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

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

Form Approved OMB No. 0910-0297
Expiration Date 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

AstraZeneca LP
725 Chesterbrook Blvd.
Mailstop E3-C
Wayne, PA 19087

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 695-1008

3. PRODUCT NAME
ENTOCORT™ Capsules (budesonide modified-release capsules)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO ____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4060

6. LICENSE NUMBER / NDA NUMBER

NDA No. 21-324

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO
(See reverse if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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Washington, DC 20201

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[signature]	Executive Director, Regulatory Affairs	JAN 1 2 2001

FORM FDA 3397 (5/98)
AstraZeneca Edition

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 21-234

Drug: Entocort EC (budesonide) Capsules

Sponsor: AstraZeneca LP

Material Reviewed

Submission Date(s): August 2, 2001, draft labeling

Receipt Date(s): August 2, 2001

Background and Summary Description: NDA 21-324, submitted January 24, 2001, provides for Entocort EC (budesonide) Capsules in the treatment of mild to moderate active Crohn's Disease. The application was approvable on July 24, 2001, pending the submission of revised draft labeling (in particular, to include an acceptable tradename) identical to that attached to the action letter, as well as a safety update. The applicant fully responded to the July 24, 2001 approvable letter with an August 2, 2001 submission. The August 2, 2001 resubmission contained the revised draft labeling that is the subject of this review.

Review

Note: The applicant's additions (relative to what was requested in the approvable letter) are indicated by underlined text. The applicant's deletions (relative to what was requested in the approvable letter) are indicated by a strikethrough.

1. Package Insert:
   a. The submitted draft package insert **(no code)** was compared to the draft package insert that accompanied the approvable letter. In addition to minor, editorial revisions, the following changes have been made:

      i. ~~[redacted]~~

      This revision is grammatically incorrect. The applicant should be requested to retain the former wording.

      ii. HOW SUPPLIED section: The applicant has retained reference to the "CIR"

imprint.

This is an acceptable revision.

(Prior to the July 24, 2001 approvable action, the Division asked the firm to delete the "CIR" imprint from budesonide capsules, based on a recommendation in the July 10, 2001 chemistry review. Accordingly, reference to "CIR" was deleted from the HOW SUPPLIED section of the draft package insert that accompanied the approvable letter.

In a July 30, 2001 submission, however, the applicant indicated that it has already amassed launch quantities of budesonide capsules bearing the "CIR" imprint. The firm requested nine months to implement the Division's request to remove the imprint, and the request was granted. (See August 8, 2001 clinical review.) Given that the HOW SUPPLIED section of the package insert should accurately describe the appearance of the capsules currently in the supply chain, reference to the imprint will be retained for now. Reference to the imprint will be deleted from the package insert once the imprint has been removed from the capsule.)

b. At the time of the approvable action (and subsequent resubmission), the applicant had not yet submitted an acceptable tradename. Accordingly, the revised draft labeling contained in the August 2, 2001 resubmission used the word "Tradename" throughout the labeling. In an August 15, 2001 review, the Office of Post-Marketing Drug Risk Assessment recommended that the sponsor use the proprietary name "Entocort EC," provided there were no objections to this tradename from the Division's chemistry group. Dr. Liang Zhou, Chemistry Team Leader, has indicated that the tradename is acceptable, accordingly, **the applicant should be requested to replace all instances of the word "Tradename Capsules" or "Tradename (budesonide) Capsules" with "Entocort EC (budesonide) Capsules" throughout the budesonide labeling.**

2. Patient Package Insert: The submitted draft patient package insert (**no code**) was compared to the draft patient package insert that accompanied the approvable letter. They are identical in content. **However, the applicant should be advised to revise this labeling to include reference to the tradename "Entocort EC."**

3. Immediate Container and Carton Labeling: The draft labels described below (**no codes**) were compared to the draft labels that were the basis for the approvable action. They are identical in content.

   a. 3 mg Capsule, 100 count immediate container label
   b. 3 mg Capsule, 6 count immediate container label (physician's sample package)
   c. 3 mg Capsule, 12 count carton label (physician's sample package)

The applicant should be advised to revise this labeling to include reference to the tradename, "Entocort EC."

Conclusions

The submitted labeling is acceptable, and this NDA can be approved (from a labeling perspective). The recommendations described above will be conveyed to the applicant with the action letter.

Regulatory Health Project Manager

cc:
HFD-180/Division Files
HFD-180/Original NDA
HFD-180/McNeil

Drafted: mm/September 5, 2001
RD Init: LTalarico 9/5/01
LZhou 9/5/01
RFrankewich 9/5/01
HGallo-Torres 9/5/01
Final: September 5, 2001

APPEARS THIS WAY
ON ORIGINAL

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/s/

Melodi McNeil
9/5/01 06:52:14 PM
CSO

Lilia Talarico
9/6/01 05:51:54 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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

Draft Labeling

48 pages = 21 pages + 27 pages

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

5 pages Draft

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

8/15/01

Date: 8/8/01

To: Lilia Talarico M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

From: Hye-Joo Kim, Pharm.D.
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment, HFD-400

Through: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment, HFD-400

CC: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Entocort EC (Budesonide Capsules)
NDA 21-324
Consult #01-0119-3

This memorandum is in response to a July 30, 2001 request from your Division for a review of the proprietary names, Entocort EC,

The sponsor, AstraZeneca, originally submitted the proposed name, Entocort. OPDRA completed a Proprietary Name Review for this product on April 3, 2001 and did not recommend the use of the proprietary name, Entocort. The primary concerns raised were related to one look-alike name, Endocet, which already exists in the U.S. marketplace. In reply to the OPDRA's objection of the name, Entocort, the sponsor proposed two alternate proprietary names: The modifiers, , were used to express the extended-release formulation of the proposed product. We agreed with the sponsor that adding a modifier to the proprietary name, Entocort, would "make it look less like Endocet." However, based upon the biopharmaceutics reviewers comment that "the product does not 'consistently' behave as delayed or extended release, OPDRA did not recommend either proprietary name.

In reply to our objection of the name, , the sponsor proposed three alternate names: Entocort EC (first choice), (second choice), and (third choice). According to the letter dated July 26, 2001, the sponsor, AstraZeneca, proposes the name Entocort EC, for the following reasons:

1. "The suffix EC does not represent anything in particular, but it is memorable as a representation of Entocort and is consistent with its use in other products such as EC Naprosyn, another product that is characterized by pH dependent release."
2. "The suffix CD is frequently used in brand names to connote altered release and once daily dosing. One such product, Metadate CD (methylphenidate) Capsules, has a mixed release pharmacokinetic profile and does not utilize a modified release dosage form nomenclature. In this regard, it is similar to budesonide capsules.
3. Entocort BC: "The suffix in this last option simply reflects the product's established name (budesonide capsules).

We disagree with the sponsor that the "suffix EC does not represent anything in particular." The modifier "EC" is commonly interpreted as "enteric-coated" by the health professionals. There are two approved proprietary names containing the modifier "EC", including EC Naprosyn and Videx EC. Both of which are enteric-coated. According to the sponsor, Entocort EC consists of the gastro-resistant coating which "protects the granules from the gastric juice" and it "dissolves at pH > 5.5, i.e., normally when the granules reach the duodenum." However, according to the review chemist, the sponsor has not performed the USP two stage (acid and base) test to prove that the proposed product is in fact "enteric coated." In order to use the modifier "EC," the sponsor should provide "data for the enteric-coated articles procedures" as instructed by the Division's chemist.

The modifier "CD" is commonly used to represent the "extended-release" formulation of the product. Currently, there are four approved proprietary names containing the modifier "CD": Ceclor CD, Cardizem CD, Lamictal CD, and Metadate CD. All but Lamictal CD is available as an "extended release" formulation. Lamictal CD is named for its "chewable dispersible" formulation. Since Entocort is not an extended-release capsule, the modifier "CD" is unacceptable.

In regards to [redacted] the sponsor stated that the "BC" simply reflects the established name, budesonide capsules. Currently, there is no approved product name that contains the modifier "BC." However, it is a commonly used abbreviation for "birth control", "beta-carotene", "blood culture", "breast cancer", and others. The Agency discourages the use of common medical abbreviations in conjunction with proprietary names for they can and have been misinterpreted. Hence, the modifier "BC" is unacceptable.

Consequently, we recommend the sponsor to use the proprietary name, "Entocort EC" contingent upon the approval of the "enteric-coated" status.

If you have any questions or need clarification, please contact Hye-Joo Kim at 301-827-0925.

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/s/

Hye-Joo Kim
8/15/01 12:52:18 PM
PHARMACIST

Carol Holquist
8/15/01 01:14:58 PM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 7/10/01

From: OPDRA, Medication Errors Prevention, HFD-400

Through: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Entocort XR
NDA 21-324
Consult #01-0119-2

To: Lilia Talarico, Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

This memorandum is in response to a July 9, 2001 request from your Division for a re-review of the proprietary name, Entocort.

The sponsor, AstraZeneca, originally submitted the proposed name, Entocort. OPDRA completed a Proprietary Name Review for this product on April 3, 2001 and did not recommend the use of the proprietary name, Entocort. The primary concerns raised were related to one look-alike name, Endocet, which already exists in the U.S. marketplace.

In reply to the OPDRA's objection of the name, Entocort, the sponsor proposed two alternate proprietary names: Entocort XL (first choice) and Entocort XR (second choice). The modifiers, "XL" and "XR", were used to express the extended-release formulation of the proposed product. We agreed with the sponsor that adding a modifier to the proprietary name, Entocort, would "make it look less like Endocet." However, we recommended that the sponsor use the proprietary name, "Entocort XR" contingent upon the approval of the established name as "budesonide extended-release."

According to the Division's letter dated July 9, 2001, the biopharmaceutics reviewers had the following comment: the product does not "consistently" behave as delayed or extended release. Since the proposed product should be called "budesonide capsules" according to the biopharmaceutics reviewers, OPDRA no longer recommends the use of the proprietary name, Entocort XR. Without the modifier, XR, we believe that Entocort could be confused with Endocet, a currently available product. In response to OPDRA's concern about potential confusion between Entocort and Endocet, the sponsor provided the following comments:

> "The potential for confusion between the two products is minimal for a number of reasons. Endocet is a scheduled II product that would be stored in a different location than Entocort. You also note that the dosing recommendations are different for the two products. While not compelling enough to eliminate the possibility of prescribing errors, the factors do reduce such a possibility. Moreover, because Endocet is a schedule II product, "sound-alike" issues are eliminated since CII products cannot be filled by telephone order and any dispensing pharmacist would have a written order in hand before filling the prescription. Finally, to the best of our knowledge, Endocet is only available as a tablet, further reducing the potential for confusion.

Endocet is not widely dispensed product and is even less often prescribed by name. Given the distinctions between the two products noted above and the low use of Endocet (IMS prescription audit data suggest approximately 2-3 million dispensed prescriptions per year), the potential for medication errors involving confusion of Endocet with Entocort is extremely low. In addition, we anticipate the typical prescription for Entocort to be written for 90 capsules, a one-month supply. While prescriptions is in the order of 40 units. A prescription for 90 capsules of Endocet would almost certainly be questioned by a pharmacist; again, this would decrease the possibility of a prescribing error."

We disagree with the sponsor's assertion that "the potential for medication errors involving confusion of Endocet and Entocort is low." Despite the differences in dosing regimen, we cannot discount the fact that these two names, Entocort and Endocet, share a close written resemblance as demonstrated in the following prescription:

Both drugs are available for oral use; Endocet is available as tablets and Entocort is available as capsules, further increasing the risk of errors. In addition, prescriptions for these drugs could be ordered with general directions, "Use as directed," without the accompaniment of the strengths since both drugs are available in one strength. We acknowledge that Endocet is a schedule II controlled substance, and that it would most likely be stored separately from Entocort. However, this may help the pharmacists choose the correct product when dispensing, but this does not assist pharmacists or nurses correctly interpret the prescriptions. In fact, one participant from OPDRA's simulated prescription study interpreted the proposed name, *Entocort, as Endocet.* In addition, Post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Inderal	Adderall
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

We also do not agree with the sponsor that "a prescription for 90 tablets of Endocet would almost certainly be questioned by a pharmacist." The oxycodone-containing products, including Endocet, are commonly prescribed in the increments of 90 tablets or more for patients with terminal illness or chronic pain. Finally, we do not believe that 2-3 million prescription dispensed per year is considered the "low use of the Endocet." Endocet, a generic brand of Percocet, is widely recognized, prescribed, and dispensed by health professionals.

We acknowledge that the sponsor markets the proposed product with the proprietary name, Entocort, in other countries, and would like to market it in the United States with the same proprietary name. However, it is irrelevant that the sponsor wants to maintain a single trademark when the name poses a safety risk.

OPDRA does not recommend the use of the proprietary name, "Entocort".

If you have any questions or need clarification, please contact Hye-Joo Kim at 301-827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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/s/

Hye-Joo Kim
7/11/01 11:49:03 AM
PHARMACIST

Jerry Phillips
7/11/01 11:53:19 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 6/18/01

From: OPDRA, Medication Error Prevention, HFD-400

Through: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Entocort XR
NDA 21-324
Consult #01-0119

To: Lilia Talarico, Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

This memorandum is in response to a June 05, 2001 request from your Division for a review of the proprietary name, Entocort XL (first choice) and Entocort XR (second choice).

The sponsor, AstraZeneca, originally submitted the proposed name, Entocort. OPDRA completed a Proprietary Name Review for this product on April 3, 2001 and did not recommend the use of the proprietary name, Entocort. The primary concerns raised were related to one look-alike name, Endocet, which already exists in the U.S. marketplace.

In addition, the issues regarding the established name have not been resolved. The sponsor originally requested the term "modified-release" to describe the formulation of the proposed product. However, the Agency or USP did not support the use of this descriptor. Therefore, the sponsor proposed to change the descriptor from the "modified-release" to the "extended-release." The Division and USP will resolve this issue at the end of this month.

In reply to the OPDRA's objection of the name, Entocort, the sponsor proposed two alternate proprietary names: (first choice) and second choice). The modifiers were used to express the extended-release formulation of the proposed product. We agree with the sponsor that adding a modifier to the proprietary name, Entocort, will "make it look less like Endocet." The Agency has approved numerous proprietary names with the modifier. . However, for this proposed product, OPDRA prefers the modifier, , for the following reasons:

1. We disagree with the sponsor's statement that "neither of these suffixes is fanciful, and should not be confused with any prescribing instruction such as number of capsules to be dispensed." In fact, the modifier, "XL" could be misinterpreted as "40" tablets to be dispensed, since the "XL" is a Roman numeral representing the number, "40". The sponsor also acknowledged that "the average prescription for oxycodone containing products is in the order of 40 units."

2. The modifier, "XL", sounds like "excel."

3. The "XR" is a common modifier to express the extended-release formulation. There are many approved proprietary names containing the modifier "XR" for extended release formulations, including Tegretol XR, Voltaren XR, Dilacor XR, Glucophage XR, and Effexor XR.

Consequently, we recommend the sponsor to use the proprietary name contingent upon the approval of the established name as "budesonide extended-release."

If you have any questions or need clarification, please contact Hye-Joo Kim at 301-827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
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/s/

Hye-Joo Kim
6/19/01 11:02:16 AM
PHARMACIST

Jerry Phillips
6/19/01 11:08:06 AM
DIRECTOR

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 01-24-01	DUE DATE: 04-25-01	OPDRA CONSULT #: 01-0035

TO: Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH: Melodi McNeil,
Project Manager
HFD-180

PRODUCT NAME: **Entocort** (budesonide 3 mg capsules) NDA #: 21-324	MANUFACTURER: AstraZeneca

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products, OPDRA conducted a review of the proposed name, Entocort, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, Entocort.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 3, 2001

NDA NUMBER: 21-324

NAME OF DRUG: **Entocort**
(budesonide capsules)
3 mg

NDA HOLDER: **AstraZeneca**

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products for assessment of the proposed proprietary drug name, Entocort, regarding potential name confusion with other proprietary/generic drug names as well as pending names. In addition, the container label, carton, patient, and package labeling were also submitted for review of possible interventions in minimizing medication errors.

The sponsor, AstraZeneca, also markets Rhinocort Nasal Inhaler, Rhinocort AQ Nasal Spray, and Pulmocort Turbuhaler, which contain the active ingredient, budesonide, in the United States. Rhinocort is indicated for the management of symptoms of seasonal or perennial allergic rhinitis in adults and children and nonallergic perennial rhinitis in adults. Pulmicort Turbuhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma.

The sponsor, AstraZeneca, has submitted this new application, NDA 21-324, for the same active ingredient. However the proposed product will be indicated for the treatment of Crohn's disease and it will be supplied as oral capsules. The sponsor already markets this product under the proprietary name, Entocort, in Europe and other countries.

PRODUCT INFORMATION

Entocort contains the active ingredient, budesonide, and it is a synthetic corticosteroid with a high topical glucocorticosteroid (GCS) activity in combination with a substantial first-pass elimination and, thus, a low potential for systemic effects. Entocort's gastro-resistant coating protects granules from the gastric juice. Hence, the active ingredient, budesonide, reaches the primary target site for treatment of Crohn's disease, the ileum and ascending colon. Thereafter, a matrix of ethylcellulose with budesonide controls the release of the drug into the intestinal lumen in a time-dependent manner. Long-term therapy with Entocort capsules seems to affect adrenal function, but only to a small extent and a majority of patients treated for up to 12 months with 3 or 6 mg daily responds normally to ACTH. Entocort is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. The recommended adult dosage is 9 mg once daily in the morning for up to 8 weeks.

Entocort can be tapered to 6 mg daily for 2 weeks prior to complete cessation. An additional 8 weeks of treatment should be considered for those patients who do not achieve clinical improvement in 8 weeks. For children weighing 30 kg or more, the recommended starting dose is 9 mg once daily. Entocort is available as 3 mg modified-release capsules for oral administration.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Entocort to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, Entocort. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Many sound-alike and/or look-alike product names were identified in the OPDRA Expert Panel that contain "cort" as the last portion of the name. Of these products, the names, Penecort, Epicort, Kenacort, Synacort, Eldecort, Amcort, Acticort, and ——— were considered to have the most potential for confusion with Entocort. In addition, the OPDRA expert panel expressed moderate concerns regarding potential confusion between Entocort and Entolase and Antrocol. The dosage forms and usual dosing of these products appear in Table 1 (page 4).

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[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

TABLE 1

Product Name	Dosage form(s); Generic name	Usual adult dose*	Other**
Entocort	Oral capsules: 3 mg (budesonide)	9 mg QAM for 8 weeks; may taper to 6 mg daily for 2 weeks prior to complete cessation.	
Penecort	Topical cream: 30 g Topical solution: 30 and 60 mL (hydrocortisone 1%).	*No longer marketed.*	S/A per OPDRA
Epicort	Topical cream and lotion (hydrocortisone)	*No longer marketed.*	S/A, L/A per OPDRA
Kenacort	Oral tablets: 4 mg and 8 mg Oral syrup: 4 mg per 5 mL (triamcinolone)	*No longer marketed.*	S/A per OPDRA
Synacort	Topical 1% cream: 15, 30, and 60 g Topical 2.5% cream: 30 g	*No longer marketed.*	S/A per OPDRA
Eldecort	Topical cream: 15 and 30 g (hydrocortisone 2.5% cream)	*No longer marketed.*	S/A, L/A per OPDRA
Acticort	Topical lotion: 60 mL (hydrocortisone 1%)	*No longer marketed.*	S/A per OPDRA
Amcort	Injection: 40 mg/mL, 5 mL (triamcinolone)	*No longer marketed.*	S/A per OPDRA
Antrocol	Atropine sulphate and Phenobarbitone Elixir	*No longer marketed.*	S/A per OPDRA
Entolase	Pancrelipase	*No longer marketed.*	L/A, S/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

****NOTE: This review contains proprietary and confidential information that should not be released to the public.****

DDMAC did not have any concerns about the name with regard to promotional claims.

B. STUDY CONDUCTED BY OPDRA

1. Methodology

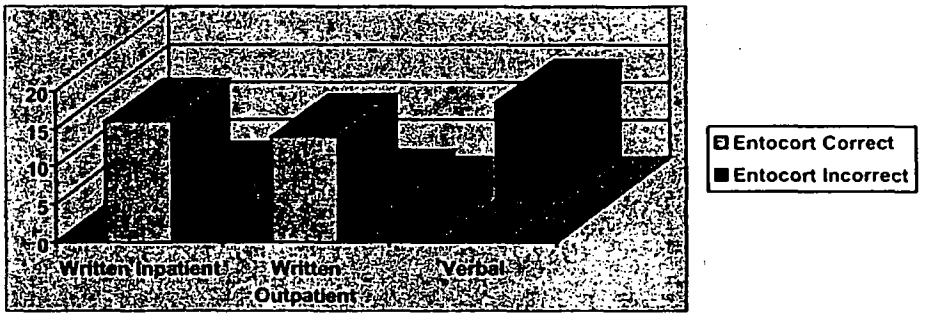
Three separate studies were conducted within FDA, to determine the degree of confusion of with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Entocort. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Entocort	
Outpatient: Entocort 3 mg Sig: 3 caps QD #90	*Outpatient:* Entocort 3 mg Take 3 capsules daily. #90
Inpatient:: Continue Entocort 9 mg QAM.	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Entocort" response	Other response
Written: Inpatient	28	18 (64 %)	16 (89 %)	2 (11 %)
Outpatient	28	15 (53 %)	14 (93 %)	1 (7 %)
Verbal: Outpatient	30	13 (43 %)	0 (0 %)	13 (100 %)
Total:	86	46 (53 %)	30 (65 %)	16 (35 %)



Among participants in the two written prescription studies for Entocort, 3 of 33 respondents (9 %) interpreted the name incorrectly. *One respondent from the inpatient written study interpreted the name incorrectly as "Endocet," a currently marketed product.* Other incorrect responses were *"Endocert" and "Entocart."*

Among participants in the verbal prescription study for Endocort, 13 of 13 (100 %) participants interpreted the name incorrectly. However, all of the incorrect name interpretations were phonetically similar to the proposed name, Entocort. Seven participants interpreted the name as *"Intercort."* Other incorrect responses were *"Intercourt," "Intecort," "Intacort," "Intocort," and "Intracort."*

C. SAFETY EVALUATOR RISK ASSESSMENT

We conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. *In this case, there was a suggestion that Entocort could be confused with Endocet.* One respondent from the inpatient written study provided *Endocet* as an interpretation. Although there are limitations to the predictive value of these studies, primarily due to the small sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Endocet is bioequivalent to Percocet, and each tablet contains 5 mg of oxycodone and 325 mg of acetaminophen. Endocet is indicated for the relief of moderate to moderately severe pain. The usual adult dosage is one tablet every 6 hours as needed for pain. The total daily dose of acetaminophen should not exceed 4 grams. Despite the differences in dosing regimen, we cannot discount the fact that these two names, Entocort and Endocet, share a close written resemblance as demonstrated in the following prescription:

Endocet #30 UUD Entocort #30 UUD

In addition, prescriptions for these drugs could be ordered with general directions, "Use as directed," without the accompaniment of the strengths since both drugs are available in one strength. We acknowledge that Endocet is a schedule II controlled substance, and that it would most likely be stored separately from Entocort. However, this may help the pharmacists choose the correct product when dispensing, but this does not assist pharmacists or nurses correctly interpret the prescriptions.

In reviewing the proprietary name, Entocort, the expert panel identified **Penecort, Epicort, Kenacort, Synacort, Eldecort, Acticort.** ——— , and **Amcort**, as most problematic with the potential for name confusion. In addition, there was concern that Entocort closely resembles **Entolase** and ———. However, the products, **Penecort, Epicort, Kenacort, Synacort, Eldecort, Acticort, Entolase,** ——— , and **Amcort**, are no longer marketed in the United States. [redacted]

——— A review of recent editions of standard references (*Micromedex, Facts and Comparison, PDR, and Orange Book)* revealed either no listing or a notation that the products had been withdrawn. However, the manufacturers were contacted to confirm the discontinuation of the above products. Therefore, confusion between the proposed product, Entocort, and the above products seems unlikely.

The AstraZeneca manufactures two products, Rhinocort and Pulmicort, that contain the same active ingredient as the proposed product, Entocort. However, Rhinocort is available as nasal inhalers and is indicated for the allergic rhinitis. Pulmicort is available as turbuhaler and is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. Since the proposed product, Entocort, is indicated for the treatment of Crohn's disease, an alternate proprietary name is appropriate. If the proprietary names, Rhinocort or Pulmicort, are used for this product, the practitioners could use Entocort incorrectly to treat allergic rhinitis or asthma.

We searched the *FDA Adverse Event Reporting System (AERS)* database. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "hydrocortisone&," "triamcinolone%,", "Penecort%," "Kenacort%," "Synacort%," "Eldecort%," "Acticort%," and "Amcort%." This search strategy retrieved zero medication error reports involving name confusion among these products.

III. COMMENTS TO BE SUPPLIED TO THE SPONSOR

OPDRA does not recommend the use of the proprietary name, *Entocort.* We acknowledge that the sponsor, AstraZeneca, markets the proposed product with the proprietary name, *Entocort*, throughout Europe and other countries, and would like to market it in the United States with the same proprietary name. However, in reviewing the proprietary name *Entocort*, the primary concerns raised were related to one look-alike name that already exists in the U.S. marketplace (*Endocet*). OPDRA's simulated prescription study identified *Endocet* to have the potential for confusion with Entocort. One participant interpreted the proposed name, *Entocort, as Endocet.*

Endocet is bioequivalent to Percocet, and each tablet contains 5 mg of oxycodone and 325 mg of acetaminophen. Endocet is indicated for the relief of moderate to moderately severe pain. The usual adult dosage is one tablet every 6 hours as needed for pain. Despite the differences in dosing regimen, we cannot discount the fact that these two names, Entocort and Endocet, share a close written resemblance as demonstrated in the following prescription:

Endocet #30 UUD Entocort #30 UUD

In addition, prescriptions for these drugs could be ordered with general directions, "Use as directed," without the accompaniment of the strengths since both drugs are available in one strength. We acknowledge that Endocet is a schedule II controlled substance, and that it would most likely be stored separately from Entocort. Post-marketing experience has demonstrated errors occurring between Class II controlled substances and non-scheduled drug products. Such examples include:

Inderal	Adderall
Demerol	Desyrel
Codeine	Iodine
Codeine	Cardene
Codeine	Lodine
OxyContin	Oxybutynin

IV. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container label, the carton labeling, the patient labeling, and the package insert of Entocort, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user errors.

A. GENERAL COMMENT

Each Entocort capsule contains 3 mg of budesonide in the form of gastro-resistant, delayed, and extended release granules. Hence, the name, "Budesonide modified-release capsule," is used by the Sponsor to described the proposed product. According to Dan Boring of the Labeling and

Nomenclature Committee, "the term 'modified release' has never been applied as a descriptor in a USP monograph nor has the Agency approved any product using 'modified release' as the FDA-designated established name. Therefore, there is no Agency or USP support for using this modifier as the established name." He recommends the name to express both mechanisms: *budesonide delayed and extended-release capsules*. However, Yana Mille has suggested that USP has used only the term "extended-release" in similar scenarios in the past and is not "aware of any case where dual references (delayed and extended) have been permitted in a name." / recommendation, the sponsor

B. CONTAINER LABEL

1.

3

C. CONTAINER LABEL-PROFESSIONAL SAMPLE

IV. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name, "Entocort".

B. OPDRA recommends implementation of the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

Hye-Joo Kim
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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/s/

Hye-Joo Kim
4/27/01 02:51:16 PM
PHARMACIST

Jerry Phillips
4/27/01 03:11:09 PM
DIRECTOR

I. Patent Information

The patent information for Entocort™ capsules (budesonide modified-release capsules) is provided in this section. One (1) patent has been identified as pertinent to the capsule formulation of Entocort™ and its indication for the treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon.

Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2).

Patent No.	Date of Patent Expiry	Type of Patent	Patent Owner	Authorized Representative to Receive Notice of Patent Certificate
5,643,602	1 July 2014	Drug product	Aktiebolaget Draco	AstraZeneca LP

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II. Patent Declaration Statement

DECLARATION

The undersigned declares that U.S. Patent Number 5,643,602 covers the Entocort™ capsule formulation. This product is the subject of this application for which approval is being sought.

Anthony F. Rogers
Vice President, Regulatory Affairs
AstraZeneca LP

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EXCLUSIVITY SUMMARY for NDA # 21-324_____ SUPPL # N/A

Trade Name Entocort EC Generic Name Budesonide
Applicant Name ASTRAZENECA LP HFD- 180
Approval Date October 2, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-233 Rhinocort Nasal Inhaler

NDA # 20-441 Pulmicort Turbuhaler

NDA # 20-746 Rhinocort Nasal Spray

NDA# 20-929 Pulmicort Respules

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 08-3027

Investigation #2, Study # 08-3001

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 08-3027

Investigation #__, Study # 08-3001

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /__/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_x__/ Explain ____ ! NO /___/ Explain _____

Conducted ex-US by applicant _____

_____ ! _____

Investigation #2

YES /_x_/ Explain _____ ! NO /___/ Explain _____

_Conducted ex-US by_____ ! _____

_applicant_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____ _____
Signature of Preparer Date
Title:_____

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Victor Raczkowski
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I. DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that in connection with this application, AstraZeneca LP (formerly Astra Phamraceuticals, L.P. until June 1, 1999 and also known as Astra Merck, Inc. Until July 1998) did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

Gary P. Horowitz, Ph.D.
Executive Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 5, 2001

APPLICATION NUMBER: NDA 21-324, budesonide capsules

BETWEEN:

Name:	Barbara Blandin, Regulatory Affairs Joanne Curley, Director, Operations CMC Strategy Gary Horowitz, Ph.D., Regulatory Affairs Paul Rogers, Product Director Renee Yancey, Manager, Operations CMC Strategy
Phone:	(610) 722-7712
Representing:	AstraZeneca LP

AND

Name:	Melodi McNeil, Regulatory Health Project Manager Liang Zhou, Ph.D., Chemistry Team Leader Ray Frankewich, Ph.D., Chemistry Reviewer Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Extension of Expiry

BACKGROUND: NDA 21-324 provides for budesonide capsules in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon. The application was approvable July 24, 2001. The firm fully responded to the approvable letter with an August 2, 2001 submission. The user fee goal date is October 2, 2001.

Prior to the July 24, 2001 approvable action, the firm was informed that submitted stability data were sufficient to justify an 18 month expiry period. In an August 16, 2001 correspondence the applicant requested a teleconference to discuss the best way to extend the expiry period.

TODAY'S PHONE CALL: The Division's chemistry representatives conveyed the following information to the firm:

1. The previously conveyed 18-month expiry period stands for now.

2. To extend the expiry period after the NDA is approved, the firm should submit 18-month data from the commercial drug product batches, with notification to the Division in a CBE-0 supplement. (The chemistry reviewer acknowledged that normally, the Division is informed of these kinds of changes in the annual report. However, he said that a CBE-0 supplement was being requested in this case due to the inconsistency seen in vivo with the pilot-scale batches.)

The call was then concluded.

Melodi McNeil
Regulatory Health Project Manager

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/s/

Melodi McNeil
9/5/01 07:25:48 PM
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APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: August 16, 2001

APPLICATION NUMBER: NDA 21-324, Entocort EC (budesonide) Capsules

BETWEEN:

Name: Gary Horowitz, Ph.D., Regulatory Affairs
Phone: (610) 695-1008
Representing: AstraZeneca LP

AND

Name: Melodi McNeil, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Removal of "CIR" Imprint

BACKGROUND: NDA 21-324 provides for budesonide capsules in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon. The application was approvable July 24, 2001. The firm fully responded to the approvable letter with an August 2, 2001 submission. The user fee goal date is October 2, 2001.

Prior to the July 24, 2001 approvable action, the Division asked the firm to delete the "CIR" imprint from budesonide capsules, based on a recommendation in the July 10, 2001 chemistry review.

In a July 30, 2001 submission, however, the applicant indicated that it has already amassed launch quantities of budesonide capsules bearing the "CIR" imprint. The firm requested nine months to implement the Division's request to remove the imprint, and the request was granted. (See August 8, 2001 clinical review.)

TODAY'S PHONE CALL: I informed Dr. Horowitz that the "CIR" imprint should be removed from Entocort EC Capsules by April 23, 2002, approximately nine months from the date the firm was first asked to remove the imprint.

The call was then concluded.

Melodi McNeil
Regulatory Health Project Manager

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/s/

Melodi McNeil
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CSO

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

8/16/01

NDA 21-324

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

We acknowledge receipt on August 2, 2001 of your August 2, 2001 resubmission to your new drug application (NDA) for budesonide capsules.

This resubmission contains additional labeling and safety update information submitted in response to our July 24, 2001 action letter.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is October 2, 2001.

If you have any questions, call me at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Melodi McNeil
8/16/01 11:54:48 AM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: August 1, 2001

APPLICATION NUMBER: NDA 21-324, budesonide capsules

BETWEEN:

Name:	Barbara Blandin, Regulatory Affairs
Phone:	(610) 695-1540
Representing:	AstraZeneca LP

AND

Name:	Melodi McNeil, Regulatory Health Project Manager Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Safety Update Report

BACKGROUND: NDA 21-324 provides for budesonide capsules in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon. The application was approvable July 24, 2001, pending (among other things) a safety update report with the content and format as specified in the approvable letter.

In a July 24, 2001 correspondence the applicant proposed an alternate format for the safety update. Specifically, they proposed a safety update that will cover the timeframe of January 1, 2001 through June 30, 2001, and contain the following:

1. Copies of all Clinical Study Reports completed during the reporting period;

2. An update of all deaths and serious adverse events from ongoing clinical trials received by AstraZeneca during the reporting period;

3. An updated review of serious adverse events from the published literature during the reporting period; and

4. An update of postmarketing reports of deaths and serious adverse events received by AstraZeneca during the reporting period.

Drs. Ruyi He (medical officer), Hugo Gallo-Torres (medical team leader), and Lilia Talarico (division director) all reviewed the proposal and found it acceptable.

TODAY'S PHONE CALL: I informed Ms. Blandin (via voice mail) that the firm's alternate proposal for the budesonide safety update, submitted July 24, 2001, is acceptable. The call was then concluded.

_____

Melodi McNeil
Regulatory Health Project Manager

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/s/

Melodi McNeil
8/1/01 09:18:46 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: July 13, 2001

APPLICATION NUMBER: NDA 21-324, budesonide capsules

BETWEEN:

Name:	Barbara Blandin, Regulatory Affairs
Phone:	(610) 695-1540
Representing:	AstraZeneca LP

AND

Name:	Melodi McNeil, Regulatory Health Project Manager Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Revised Draft Labeling

BACKGROUND: The applicant's draft labeling (package insert, patient package insert, and immediate container/carton labeling) was revised, based on finalized reviews and additional discussions with reviewers. This revised labeling, along with four general comments, was faxed to the firm. (The revised labeling and comments that were faxed to the firm are provided in the attachment.)

TODAY'S PHONE CALL: I informed Ms. Blandin that marked-up draft labeling had just been faxed to AstraZeneca. I added the following comments:

1. The user fee goal date for this NDA is July 24, 2001. Labeling agreement (between AstraZeneca and FDA) is the only outstanding issue preventing approval.

2. FDA plans to issue a Talk Paper when this NDA is approved.

3. The firm's proposed tradename (Entocort) is unacceptable, however, FDA can approve an NDA without a tradename.

4. In contrast to the firm's claims, FDA considers this product neither delayed- nor extended-release. Accordingly, FDA is asking the firm to remove (or agree to remove) the "CIR" imprint from the budesonide capsule shell.

Note: After today's phone call, Ms. Blandin pointed out some text that was missing from the DOSAGE AND ADMINISTRATION section of the package insert. Specifically, the words "beyond 8 weeks" were inadvertently omitted from the sentence, "Safety and efficacy of TRADENAME in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon have not been established beyond 8 weeks." This correction has been made with the firm and in the appended version of the labeling.

Melodi McNeil
Regulatory Health Project Manager

General Comments:

1. According to your submission, the granules in budesonide capsules provide gastro-resistant, delayed- and extended-release properties to the formulation. However, submitted data show that the product does not exhibit these characteristics in a consistent manner. In study 08-3015, for example, 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.

2. In the [redacted] method used to study the site of uptake of budesonide, no rationale was provided in support of your position that ^{111}In pellets will have the same transit time through the GI tract as budesonide CIR pellets. Furthermore, if the enteric coating of the product is set to dissolve at pH > 5.5, it is unlikely that any delayed-release properties will last until the ileum. There is published data in fasting subjects indicating that pH in stomach and duodenum is 5.5. The pH is even higher after ingestion of food.

3. Given the information in points 1 and 2 (above) we consider this product neither delayed- nor extended-release. Accordingly, your proposal to add a suffix such as XR, XL, or SR (all of which connote an extended-release product) to your tradename is inappropriate. Thus, we reiterate our position, initially conveyed in our May 3, 2001 letter, that the tradename "Entocort" (alone) is unacceptable, because there is a potential for confusion with "Endocet," a look-alike, sound-alike name that already exists in the US Marketplace.

4. In addition, please remove (or agree to remove) the "CIR" imprint from budesonide capsules.

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

25 pages draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-324

DISCIPLINE REVIEW LETTER

5/23/01

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailstop E-3C
P.O. Box 8355
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your January 24, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for budesonide capsules.

We also refer to your submissions dated February 9, April 6, and May 1, 2001.

Our review of the chemistry, manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1. Clarify whether the 2.5% overage in the budesonide layer of the granule applies only to budesonide or to all the components of the budesonide suspension.

2. Commit to employ one batch size for the drug product that is (or will be) used for all future commercial batches. If that batch size is larger than the one used for the primary stability study ———————, be advised that it will be necessary to submit supplements to the NDA (refer to the FDA/CDER Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms).

3. Confirm that any batches of granules that are combined to form one batch will be manufactured at the same scale, with the same equipment and the same procedures.

4. Clarify whether or not the tests listed as "Additional tests performed according to USP24/NF19" on the COA for Acetyltributyl Citrate (pg. 004-001-295, vol. 1.3) are performed on every batch. If not, provide justification for this and submit procedures and validation data for any non-compendial procedures used to characterize this substance.

5. Regarding the proposed method for Assay of Methacrylic Acid Copolymer Type C 30% Dispersion (acid-base titration):

   - Demonstrate that the procedure is linear within a reasonable range of the sample size used;

- Demonstrate that the addition of [redacted] to the sample before the start of the titration does not influence the results of the assay determination;
- Explain why, in the calculation of percent methacrylic acid units, the term percent residue on evaporation (LOD) is used instead of (100 – LOD), which is used in the NF monograph.

6. Regarding the proposed testing monograph for Triethyl Citrate, NF:

   - Revise the monograph so that is complies with the changes provided for in the 2nd Supplement to USP24/NF18;
   - Clarify whether or not the Heavy Metals test is performed on every batch. If not, provide justification.

7. Regarding the acceptance testing of Polysorbate 80, clarify whether or not the NF monograph (chemical) ID tests and the test for Organic Volatile Impurities (OVI) are performed on each lot received. If not, commit to performing these tests on each lot or provide justification why this is not necessary.

8. Regarding the acceptance testing of Sugar Spheres, clarify whether or not the test for Organic Volatile Impurities (OVI) is performed on each lot received. If not, commit to performing this tests on each lot or provide justification why this is not necessary.

9. Adopt the USP monograph tests and specifications for Talc.

10. Regarding the material Antifoam M:

    - Definitively identify the substance beside poly-dimethylsiloxane as either silicon dioxide or colloidal silicic acid;
    - Provide the specific amounts of both components in the drug product formula;
    - Provide assurance that both substances meet the requirements of their current NF monographs.

11. Specifications for the gelatin capsules should be changed so that the item meets the appropriate USP Microbial Limit Tests in <61>, rather than the Ph. Eur. tests.

12. Provide a description of the process used to sample each batch of drug product for release testing. Specify the number of individual samples used in each test.

13. Resolve the following issues regarding the specifications and analytical methods used to characterize the drug product:

    - [redacted]
    - [redacted]
    - [redacted]

these peaks.

14. Clarify the statement (pg. 004-001-127, vol. 1.3) that the holding time of the capsules in the bulk package is included in the total shelf life of the product. Also provide data that establishes the maximum holding time at 10 months at 25° C, and provide data that establishes that the aluminum bag provides adequate protection from moisture.

15. Provide the specific regulation within 21 CFR 177.1520 that describes the product contact surface of the aluminum bag used for bulk packaging of the drug product.

16. For each packaging component tested by AstraZeneca TPS, provide the sampling plan used to obtain samples and the specifications and acceptance criteria used in the testing.

17. Provide the name and address of the manufacturer and supplier used in each market package. Provide the specific regulation within 21 CFR 177.1520 that describes the component materials contains this information.

18. Explain whether or not a package consisting of a sample carton of 12 capsules is planned for this dosage form (labeling for this package is provided on pg. 002-001-273 of vol. 1.1). If so, complete information should be provided describing it.

19. The maximum justifiable expiration period for the drug product appears to be 12 months, based on the real-time primary stability data. Data from pilot and intermediate scale-up batches

20. Establish a moisture specification for both release and stability testing of the drug product. Stability stress testing indicates the granules are degraded by heat and humidity; the fact that the dessicant canisters absorb large amounts of moisture does not eliminate the possibility that the granules may also absorb moisture.

21. [redacted]

22. [redacted]

23. [redacted]

24. Revise Tables 6 and 7 (describing Intermediate Precision) in Validation Report No. 850-RD-0355-02 for the Drug Release methods such that the personnel and equipment performing the experiments is discernable.

25. Propose alternate proprietary and established names for this drug.
Refer to the May 3, 2001 Discipline Review Letter regarding the inadequacy of the currently proposed names.

26. Regarding the final sentence of the second paragraph of the DESCRIPTION section in the proposed package insert ("Its partition coefficient between..."), confirm that the pH value is correct and explain the reference to ionic strength. (Other labeling comments will be conveyed separately.)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
5/23/01 11:49:20 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-324

DISCIPLINE REVIEW LETTER

5/3/01

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailstop E-3C
P.O. Box 8355
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your January 24, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for budesonide capsules.

We have completed our review of your proposed proprietary name, Entocort, and find it unacceptable because there is a potential for confusion with "Endocet," a look-alike, sound-alike name that already exists in the US marketplace. Endocet contains 5 mg of oxycodone and 325 mg of acetaminophen. We acknowledge that as a Scheduled II controlled substance, Endocet may be stored separately from budesonide. However, there have been several cases of confusion between Schedule II controlled drug products and non-scheduled drug products in the post-marketing setting. Also, though the two products have different dosing recommendations, the possibility exists that both products could be prescribed with the general directions, "Use as directed," further increasing the chance of confusion.

In addition, you have proposed to describe the budesonide drug product as a "modified-release" capsule. The term "modified-release" has never been applied as a descriptor in a USP monograph, nor has the Agency approved any product using "modified-release" as the FDA-designated established name. Therefore, there is no Agency or USP support for using this term. We advise you to resolve this nomenclature issue with USP, and authorize the Agency to consult with USP on this matter, prior to approval.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC 2, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
5/3/01 12:40:18 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

April 26, 2001

AstraZenaca LP
725 Chesterbrook Boulevard
Wayne, PA 19087

Attention: Gary Horowitz, Ph.D.
Executive Director, Regulatory Affairs

Dear Dr. Horowitz:

Reference is made to the orphan drug application dated August 14, 2000, submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of budesonide as an orphan drug (application #00-1386).

We have reviewed your request for orphan-drug designation of budesonide for the treatment of mild to moderate active Crohn's Disease involving the ileum and ascending colon. We are pleased to learn of your clinical development of Entocort™ CIR (budesonide) for the treatment of Crohn's disease. Entocort™ CIR (budesonide) may prove to be a unique glucocorticoid treatment in that it may provide patients with the beneficial effects of a steroid therapy with fewer side effects. As a result, physicians are likely to administer Entocort™ CIR (budesonide) to Crohn's disease patients far more readily as compared to the currently approved glucocorticoids. It is conceivable that the drug will be used as a treatment of choice for Crohn's disease. Therefore, the target population of this drug should include all patients with Crohn's disease, and not only those whose disease is currently managed by systemic steroid therapy as you have indicated. According to your estimate, Crohn's disease affects approximately 370,300 patients in this country, which exceeds the numerical threshold of 200,000 for the purposes of orphan drug designation.

Consequently, while the development of Entocort™ CIR (budesonide) shows promise to be an effective therapy in the treatment of Crohn's disease, the population of patients having Crohn's disease is over the threshold of 200,000. Consequently, your request for orphan drug designation for Entocort™ CIR (budesonide) for the treatment of mild to moderate active CD involving the ileum and ascending colon cannot be granted.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

cc:
HF-35/OP File #00-1386
HF-35/Chron
HF-35/SDonahoe
JFritsch 04/20/01

APPEARS THIS WAY
ON ORIGINAL

TO: Barbara J. Blandin
Associate Director
Regulatory Affairs
AstraZeneca

TEL: 1-(610)-695-1540
FAX: 1-(610)-578-8213

From: Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician
DB2/CDER/FDA
TEL: 1-301-827-3089
FAX: 1-301-443-9279

Date: March 30, 2001

RE: CDAI remission status Data listing for Entocort NDA#21-324

The data listing in the NDA submission and the electronic data submission appear to be consistent. However, it seemed that the total number of patients who had CDAI score <=150 may or may not be the same as what are presented in the summary table of the NDA reports.

For each of the five (08-3001, 08-3002, 08-3013, 08-3025, 08-3027) studies in NDA#21-324, please provide a hard copy data listing you used in the summary table of the NDA reports and an electronic version if possible. The data listing (sorted by patient ID) should include the following information.

Study#, patient#, treatment assigned, days from randomization, study_co, CDAI value after week-8 and the corresponding remission indicator (the primary efficacy variable).

If you have questions, I can be reached at 1-301-827-3089.

Thank you.

Cc: Huyi He, M.D.
Melody McNeil, Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-324

INFORMATION REQUEST LETTER

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087

Dear Dr. Horowitz:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entocort (budesonide) Capsules.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Provide a rationale for not including microbial testing as part of the specifications for either the budesonide granules or the finished drug product.

2. Establish a moisture specification for the drug product (the granules).

3. Please provide the six, nine, and 12 months stability data for primary batches BB1253 (start date: May 15, 2000); BB1255 (start date: May 29, 2000); and BD1264 (start date: July 10, 2000) when they become available. According to the NDA, you only plan to submit the six month data. Please include data for both packaging configurations (100 count HDPE bottle with tamper-evident CRC cap, and 6 count HDPE bottle with tamper-evident (non-CRC cap).

4. Volume 1.3, pages 004-001-133 to 004-001-135 contain tables documenting your stability protocols. In these tables, the designations "P" (planned analysis) and "X" (reserve samples) are used for the test stations at which analyses are planned. Please provide additional clarification as to what these designations mean.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products,
(HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Liang Zhou
3/16/01 01:34:18 PM
The IR letter needs to be issued due to a p-drug status while the CMC review has not being completed yet

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-324

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
Executive Director, Regulatory Affairs
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087

Dear Dr. Horowitz:

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

Name of Drug Product: Entocort (budesonide) Capsules

Review Priority Classification: Priority (P)

Date of Application: January 24, 2001

Date of Receipt: January 24, 2001

Our Reference Number: NDA 21-324

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 24, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 24, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application.

In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Melodi McNeil
2/23/01 11:55:42 AM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 20, 2001

APPLICATION NUMBER: NDA 21-324, budesonide capsules

BETWEEN:

Name: Gary Horowitz, Ph.D., Regulatory Affairs
Phone: (610) 695-1008
Representing: AstraZeneca LP

AND

Name: Melodi McNeil, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Information Requests

BACKGROUND: NDA 21-324 was submitted January 24, 2001 and provides for budesonide capsules for the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

Upon completion of my administrative review, I conveyed the following requests to the applicant.

TODAY'S PHONE CALL: I asked Dr. Horowitz to provide to provide the following (or indicate where they were located in the NDA):

1. Color mock-ups of the immediate container and carton labeling (one archival copy, two technical copies);

2. A corrected table of contents (the submitted table of contents indicates the international data sheet is at p. 002-001-336k, however, it is not);

3. A table of all controlled clinical studies, in accordance with the Guideline for the Format and Content of the Summary for New Drug And Antibiotic Application; and

4. Subgroup analyses (e.g., age, race, and gender).

The call was then concluded.

_____

Melodi McNeil
Regulatory Health Project Manager

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/s/

Melodi McNeil
7/16/01 02:00:01 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 25, 2000
TIME: 8:30-10:00 A.M.
LOCATION: Conference Room "M" (Parklawn)
APPLICATION: [redacted]
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Dr. Lilia Talarico, Division Director

MEETING RECORDER: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Lilia Talarico, Director
Dr. Steven Aurecchia, Deputy Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Lawrence Goldkind, Medical Officer
Dr. Robert Prizont, Medical Officer
Dr. Jasti Choudary, Pharmacology Team Leader
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)
Dr. Suliman Al-Fayoumi, Biopharmaceutics Reviewer

Division of Biometrics II (HFD-715)
Dr. Thomas Permutt, Acting Statistical Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
AstraZeneca LP

Dr. Staffan Edsbacker, Human Pharmacology
Dr. Claes Engelbrecht, Preclinical Toxicology
Dr. Jose Gallo, Biostatistics
Dr. Gary Horwitz, Regulatory Affairs
Ms. Donna Kipphorn, Regulatory Affairs
Dr. Jeffery Levine, Clinical Physician
Dr. Anders Persson, Clinical Program Leader
Mr. Paul Rogers, US Product Team Leader
Dr. Tore Persson, Global Project Statistician

BACKGROUND: [redacted] was submitted by Astra USA, Inc. (now AstraZeneca LP) on December 14, 1994 to investigate budesonide controlled ileal-release (CIR) Capsules for the

treatment of Crohn's Disease. The FDA held an End of Phase 2 meeting with the sponsor on May 18, 1995 (minutes available).

In a March 30, 2000 submission, the sponsor requested a meeting to discuss submission of an NDA for Entocort CIR (budesonide) Capsules in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

MEETING OBJECTIVE: To discuss submission of an NDA for Entocort CIR (budesonide) Capsules in the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

DISCUSSION POINTS: The sponsor's March 30, 2000 contained specific questions for the agency to answer. These questions are reproduced below in regular type; the agency's responses follow in bold type.

1. **USE OF PENTASA® AS CONTROL (CLINICAL)**

   Q.: Study No. 08-CR-3027 employed Pentasa® as a control group. Pentasa is widely used in the treatment of Crohn's disease. Pentasa is not approved in the United States for Crohn's disease, although it is approved for treatment of ulcerative colitis. The sponsor believes it reasonable to assume that Pentasa would have performed no worse than placebo in Crohn's disease, and therefore, it is a valid control for this study. Does the agency concur?

   Agency Response:

   We concur with the use of a mesalamine product as a control in this study. Superior efficacy of budesonide to mesalamine must be demonstrated. Safety profiles will also be compared, including adverse events associated with the use of mesalamine (e.g. diarrhea). Also note: A positive result in Study 08-CR-3027 does not mean that you will be able to make a labeling or promotional claim of superiority to mesalamine. (Agency representatives added that the sponsor will be expected to provide details about the formulation of the mesalamine comparator used in this study, in particular how it compares to currently approved US formulations.)

2. **ADEQUACY OF CLINICAL PROGRAM (CLINICAL PHARMACOLOGY/CLINICAL)**
   Q.: Is the clinical program, as currently outlined and considering question #1, adequate to support the filing of Entocort® (budesonide CIR) capsules for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon?

   Agency Response: The clinical program as outlined is adequate for NDA submission. (Note: FDA representatives noted several potential review concerns, based on their review of the background package. These issues included the relevance of the desired indication [Crohn's

Disease limited to the ileum and ascending colon] given the fact that Crohn's is most frequently a disease of the entire gastrointestinal tract.)

3. **CROSS REFERENCING BUDESONIDE NDA (REGULATORY)**
Q.: Budesonide, the active ingredient in Entocort capsules, is approved in the United States in a different dosage form for asthma and allergic rhinitis. Are the non-clinical data from the approved NDAs, incorporated by reference, along with the three budesonide CIR primate studies adequate to support filing of the proposed NDA?

Agency Response:

a. **Your proposal is acceptable, provided you include detailed summaries of the non-clinical studies from other approved NDAs in the Non-clinical summary portion of the planned budesonide CIR Capsules NDA.**

b. **In addition to the full reports of the chronic toxicology study in monkeys, the budesonide CIR NDA should also include full reports of chronic toxicology portions of the studies in mice (reference 29 in the background package), and rats (references 30, 31, and 32).**

c. **Any new non-clinical oral and in vitro toxicology study data not previously submitted to an already approved NDA should be provided in detail in the budesonide CIR NDA.**

d. **Provide all preclinical and clinical metabolism data generated after oral administration.**

e. **Provide all mutagenicity data.**

4. **FAST TRACK DEVELOPMENT/EXPEDITED REVIEW (CLINICAL/REGULATORY)**
Q.: The sponsor believes that mild to moderate active Crohn's disease involving the ileum and/or the ascending colon is associated with morbidity that has a substantial impact on day-to-day functioning and as such represents a serious condition. Furthermore, treatment of this condition with Entocort capsules represents a significant therapeutic gain compared to currently marketed products. Does the agency concur that Entocort capsules for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon represents a valid condition for designation for fast track development and that it may qualify for priority review of the proposed NDA?

Agency Response:

a. **Fast Track: Fast track designation applies primarily to a drug development program. Given the relatively late stage of development of budesonide CIR**

capsules for the treatment of active Crohn's Disease, fast track designation does not seem applicable at this time. However, if you still wish to pursue fast track designation, you may request formal fast track designation as described in the Guidance for Industry, entitled "Fast Track Drug Development Programs-Designation, Development, and Application Review."

b. **Priority Review: Priority review is a possibility, however, a final determination will be made at the time of filing.**

5. ORPHAN DRUG STATUS (CLINICAL/STATISTICS)

Q.: Based on the proposed indication, treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and prevalence estimates for this condition, the sponsor is interested in pursuing Orphan Drug status. Can the agency suggest other factors that may affect designation of Orphan Drug status?

Agency Response: The Division does not have any other suggestions as to factors that may affect designation of Orphan Drug status. For additional information, please refer to 21 CFR part 316 or contact the Office of Orphan Product Development. Information on how to apply for orphan drug designation is available at www.fda.gov/orphan/designat/apply.htm.

6. PEDIATRIC RULE (CLINICAL/REGULATORY)

Q.: The sponsor has conducted a pharmacokinetic study in children with Crohn's disease that will show that systemic exposure (AUC) to budesonide in pediatric patients is similar to that observed in adults. Using published literature, the sponsor will demonstrate that the clinical manifestations and treatment strategies for Crohn's disease in children is similar to those for adults. Would this body of data be adequate to support the requirements for pediatric information described in the Pediatric Final Rule (21 CFR 314.55(a)). In addition, the sponsor seeks to terminate the ongoing pediatric clinical study (SD-008-3037) due to slow enrollment. Does FDA agree with the sponsor's decision?

Agency Response:

a. **Please provide more details about the ongoing pediatric clinical trial, including its endpoints.** (The sponsor indicated that the primary endpoint of the study is improvement in CDAI score. They added that the purpose of the study is to compare the safety and efficacy of budesonide versus prednisolone in pediatric patients.)

b. **Please provide your explanation as to why enrollment in the pediatric study has been slow.** (According to the firm, budesonide CIR is approved in Europe,

and parents there are reluctant to enroll their children in a study in which there is a 50% chance of receiving prednisolone. After hearing the firm's rationale, the FDA agreed with the sponsor's plans to terminate this study.)

c. **Based on available information, your proposed body of data is not adequate to support the requirements for pediatric information described in the Pediatric Final rule. Although the efficacy of budesonide may be similar in adults and children, there is no information to demonstrate that the safety of this compound is similar in adults and children.** (Note: The subject of exactly what pediatric data would be expected in an NDA submission was discussed, but no conclusions were reached. The FDA will hold internal discussions as to the kinds of pediatric data that should be available at the time of NDA submission versus what can be deferred until later.)

In addition, the following general comments were conveyed:

1. Clinical Pharmacology:

   a. **All studies submitted in the clinical pharmacology section of the budesonide CIR capsule NDA should be clearly identified with regard to whether they have been previously submitted. Please also reference the application to which results of these studies have been submitted.**

   b. **Regarding data from the study of budesonide in hepatically impaired patients, please analyze these data according to the degree of liver failure (e.g., severe, moderate, mild).**

   c. **We note that the pharmacokinetic database includes only two elderly subjects. Adequate support for the safety and efficacy of budesonide CIR capsules in this age group may need to come from the clinical database.**

2. Clinical:

   a. **Please provide any available data which addresses the issue of whether budesonide has long-term effects on pituitary-adrenal function, bone density, or immune system.**

   b. **The exact indication you are seeking is unclear. Various parts of the background package mention both treatment of active Crohn's Disease and induction of remission. Note that there are no guidelines currently available (for example, about endpoint definition) on the induction of remission claims. Further, the data in the background package do not support an induction of remission claim.** (The firm clarified that they will be seeking a claim for the treatment of active [ileal and ascending colon] Crohn's

Disease.)

3. **Financial Disclosure:**

   a. **Any marketing application for budesonide CIR capsules is required to contain a list of clinical investigators who conducted certain clinical studies and certify and/or disclose certain financial arrangements.**

   b. **For additional information, please refer to the draft guidance document entitled "Financial Disclosure by Clinical Investigators." (This guidance is available at www.fda.gov/oc/guidance/financialdis.html.) Please also refer to 21 CFR 54.**

Minutes Preparer: /S/ 6/9/

Chair Concurrence: /S/ 2-c

APPEARS THIS WAY
ON ORIGINAL

cc: Original
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/McNeil
HFD-180/Talarico
HFD-180/Aurecchia
HFD-180/Gallo-Torres
HFD-180/Goldkind
HFD-180/Prizont
HFD-180/Choudary
HFD-870/Al-Fayoumi
HFD-715/Permutt

Drafted by: MM/JUNE 2, 2000
Initialed by: SAl-Fayoumi 6/5/00
HGallo-Torres 6/6/00
SAurecchia 6/5/00
LTalarico 6/6/00, 6/8/00
JChoudary 6/8/00

final: June 9, 2000

MEETING MINUTES

Je1.1507

AUG 22 1995

Astra Inc.
Attention: Paul J. Damiani, PhD
P.O. Box 4500
Westborough, MA 01581-4500

Dear Dr. Damiani:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for Entocort (budesonide) Capsules.

We also refer to the End of Phase 2 meeting held on May 18, 1995, between representatives of your firm and this Agency. The following represents our summary of the meeting.

MEMORANDUM OF MEETING
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Entocort (budesonide) Capsules
End of Phase 2 Meeting
May 18, 1995

BETWEEN

Astra USA:

Michael Fox, MD-Clinical Dev., Medical & Regulatory Affairs
Dennis Bucceri-Regulatory Affairs
Lloyd Haskell, MD-Clinical Research
Jeffrey Levine, MD-Clinical Research
Paul Damiani, PhD-Regulatory Affairs
Karen Walton-Bowen-Biostatistics

Astra Draco:

Staffan Edsbacker, PhD-Human Pharmacology
Lars Goran Nilsson-Clinical Research
Tore Persson, PhD-Biostatistics
Hans Graffner, MD, PhD-Clinical Research

Food and Drug Administration, HFD-180:

Stephen B. Fredd, MD-Division Director
Robert Prizont, MD-Medical Officer
Kati Johnson-Consumer Safety Officer

Food and Drug Administration, HFD-713:

Mohammad Huque, PhD-Group Leader, Statistics

BACKGROUND

Budesonide is a glucocorticosteroid currently approved in a metered dose inhaler for the prevention and treatment of seasonal or perennial allergic and nonallergic rhinitis (Rhinocort, NDA 20-233, approved February 14, 1994). An enema formulation ——— is being investigated for the treatment and induction of remission of ulcerative colitis (UC). This IND, submitted December 14, 1994 to investigate a controlled ileal release (CIR) capsule formulation for the treatment of Crohn's Disease, contained clinical protocol 08-3025, entitled, "Budesonide Controlled Ileal Release Capsules (9.0 mg) Once and (4.5 mg) Twice Daily in Active Crohn's Disease. A Placebo-Controlled (PBO) Study". A letter was sent to the firm on March 21, 1995, containing our recommendation on the design of the study, which the firm anticipates using as one of the pivotal studies required for approval. Phase 1 and 2 studies have previously been conducted in Europe and Canada. The firm requested an End Of Phase 2 meeting to provide the Agency with an overview of their Phase 2 studies and to obtain input on Phase 3 study design.

MEETING

The firm stated that their objectives for the meeting include responding to the issues raised in the March 21, 1995 letter regarding protocol 08-3025 and obtaining Agency feedback on the acceptability of the clinical development program for the proposed indications (treatment and maintenance therapy for Crohn's Disease).

Dr. Edsbacker began with a brief discussion of the dosage form. The CIR capsule contains . The pellets are then to prevent release in the stomach. According to the firm, this enteric coating is resistant up to pH 5.5. In response to a question from Dr. Fredd, the firm stated that drug release is expected in the duodenum and jejunum, although there is no direct evidence. However, by relating drug release to plasma budesonide levels, it has been determined that the compound reaches the cecum at 2 hours post-ingestion. Dr. Fredd noted that this does not indicate precisely where, above the cecum, it is released, and suggested that barium or technetium labeled material could provide this information.

According to Dr. Edsbacker, although budesonide absorption is nearly complete, only 10-20% of the dose (as determined by studies in healthy male volunteers and patients, respectively) is available due to extensive first pass metabolism. In response to a question from Dr. Fredd, the firm said that no information in available to explain this difference. Following a 9 mg morning dose, C_{max} reaches 5-10 nmol/L after 3 to 5 hours. Although an increase in the amount of budesonide absorbed might be expected if taken concomitantly with agents affecting gastric acid secretion, the firm said that no such increase was observed when budesonide was given with omeprazole, a potent proton pump inhibitor.

Dr. Haskell stated that the firm plans Phase 3 studies to investigate both the symptomatic treatment and maintenance of Crohn's Disease and summarized the controlled Phase 2 studies conducted to date.

TREATMENT OF CROHN'S DISEASE

With regard to the treatment indication, the firm has conducted both PBO and active controlled studies. To qualify for enrollment in these studies, patients must have had a CDAI (Crohn's Disease Activity Index) score $\geq$ 200. The primary

efficacy endpoint was the percent of patients with a CDAI score ≤ 150 following 8 weeks of treatment.

Protocol 3001, conducted in Canada, was a PBO controlled study comparing daily budesonide doses of 3.0 (1.5 mg BID), 9.0 (4.5 mg BID) and 15.0 mg (7.5 mg BID). The two highest doses were administered for 8 weeks, then tapered to 6.0 mg daily (3.0 mg BID) for two weeks. The lowest dose group received PBO during the tapering phase. According to the firm, both the 9 and 15 mg daily doses were statistically significant compared to PBO for the primary efficacy variable. In response to a question from Dr. Fredd, the firm responded that 258 randomized patients were available for evaluation, and 119 discontinued, primarily due to disease deterioration. Dr. Fredd noted that using the last observation carried forward to analyze dropouts may favor budesonide. With regard to the effect on endogenous cortisol levels, the firm said that only the 15 mg dose resulted in a significant decrease in the percent of patients with a normal ACTH-stimulated cortisol response compared to PBO. Dr. Fredd reminded the firm that they should examine various subgroups (those with resections; baseline CDAI score) to ensure balance between the treatment cohorts.

Protocol 3002 was conducted in Europe and compared single daily doses of budesonide and prednisolone. Budesonide was dosed at 9 mg QD for 8 weeks, then decreased to 6 mg QD for 2 weeks; prednisolone was dosed at 40 mg daily for 2 weeks, then tapered to 5 mg daily by the end of week 10. According to the firm, budesonide was not significantly different from prednisolone for the percentage of patients achieving a CDAI ≤150 at weeks 2, 8 and 10. At week 4, prednisolone was statistically superior ($p<0.001$) to budesonide. With regard to plasma cortisone levels, budesonide had significantly less effect on basal cortisol values at 2, 4 and 8 weeks; the difference at 10 weeks was not statistically significant. The firm concluded that although prednisolone was more effective for decreasing the mean CDAI, it had a significantly greater effect on basal plasma cortisone. Since these are active controlled studies, Dr. Fredd reminded the firm that, to show the drugs were effective, an historical PBO response must be determined and be acceptable.

Protocol 3013, conducted in Europe and New Zealand, compared tapering doses of budesonide to prednisolone. According to the firm, 178 patients were randomized to the following treatment groups:

1. Budesonide, 9.0 mg QD for 8 weeks, decreased to 6.0 mg QD for 2 weeks, then decreased to 3.0 mg QD for 2 weeks.
2. Budesonide, 4.5 mg BID for 8 weeks, decreased to 3.0 mg BID for 2 weeks, then decreased to 1.5 mg BID for 2 weeks.
3. Prednisolone 40 mg QD for 2 weeks, tapering to 5.0 mg QD for weeks nine through twelve.

The firm said that there was no statistically significant differences between the treatments in the percent of patients achieving a CDAI ≤150 at week 2, 4, 8 or 12. However, Dr. Fredd noted that at each time point, BID dosing appeared inferior to QD dosing. In addition, according to the premeeting document, it appeared that the patients receiving budesonide had milder disease at baseline, and reiterated that it must be determined that the treatment groups were balanced for variables that could effect efficacy. With regard to safety, the firm said budesonide had a higher percentage of patients (p(0.001) with a normal ACTH-stimulated cortisone response at week 8.

These studies will provide safety data from 268 patients randomized to 9 mg budesonide, the proposed daily dose for the treatment of Crohn's Disease (either as a single 9 mg dose or as 4.5 mg BID). In addition, ongoing Study 3027 , comparing 9 mg QD budesonide to Pentasa Capsules (NDA 20-049, approved May 3, 1993), will provide safety information on 90 additional patients. This data combined with the data for 160 patients proposed for Study 3025, discussed below, will increase the number of patients exposed to the drug to 518. In response to a question from Dr. Fredd, the firm said that Study 3027 is designed to evaluate superiority of budesonide to a 4 gram daily dose of Pentasa [currently approved for induction of remission and the symptomatic treatment of mildly to moderately active UC].

Protocol 08-3025 was included in the initial IND submission and provided the basis for the March 21, 1995 letter. The firm stated that the objective of the study is to assess the efficacy and safety of 4.5 mg BID and 9.0 QD budesonide, compared to PBO, in patients with active Crohn's Disease affecting the ileum and/or ascending colon. Adult patients with a CDAI between 200 and 450 will be enrolled, excluding those with fistula, abscess or obstruction. The protocol will include a 3 month washout period for immunosuppressive drugs, and a 2 week washout period for other medications. The following treatment arms are proposed: budesonide 4.5 mg BID for 8 weeks followed by 3.0 mg BID for 2 weeks; budesonide 9.0 mg QD for 8 weeks followed by 6.0 mg QD for 2 weeks; and PBO. Similar to Protocols 08-3001, 08-3002, and 08-3013, the primary efficacy endpoint is defined as a decrease in CDAI to a value ≤150 following 8 weeks of therapy. While Dr. Fredd agreed that a PBO controlled study is not likely to negatively affect the firm's ability to enroll investigators (given the high PBO response for Crohn's Disease), he suggested that the firm consider adding an active control, such an another steroid. In addition, since Protocol 3013 indicates that 4.5 mg budesonide BID is inferior to 9 mg QD, he suggested that the firm consider replacing the 4.5 mg BID arm with a higher QD dose, such as 12 mg. He also suggested that the firm analyze whether any results are driven by patients who were previously on drug therapy, but who were taken off the therapy to qualify for enrollment in this study.

MAINTENANCE OF REMISSION OF CROHN'S DISEASE

The firm proceeded to discuss the controlled maintenance studies conducted to date. Protocols 3003 and 3004 were identical 52-week, double-blind, PBO controlled studies in which patients with a CDAI ≤150 at completion of a previous budesonide study were re-randomized to budesonide 3 mg or 6 mg QD, or PBO. In response to a question from Dr. Fredd, the firm confirmed that eligibility for re-randomization in this study did not require treatment with budesonide in the previous study. Efficacy endpoints were relapse rate and time to relapse; relapse was defined as an increase in CDAI of ≥60 points to a value ⟩150, or patient withdrawal due to acute disease deterioration. According to the

firm, for protocol 3003, median time to relapse was statistically significant ($p<0.05$) in patients on 6 mg budesonide (n=36, median time=180 days) compared to PBO (n=36, median time=42 days). Although the protocols provided for evaluation every 3 months, Dr. Fredd noted that if patients on PBO returned for more physician visits due to the development of symptoms, observational bias could have been injected. With regard to relapse rate, there was no statistically significant difference demonstrated between any of the treatments at either 3, 6, 9 or 12 months.

According to the firm, median time to relapse for Protocol 3004 was statistically significant ($p<0.05$) between the 6 mg dose (n=32, median time=271 days) and PBO (n=27, median time=146 days). According to the firm, treatment assignment in the treatment protocol (which determined eligibility for this study) had no effect on the relapse rate in this maintenance study. Dr. Huque commented on the potential need for multiple comparison adjustment given that there are 2 treatments and 4 periods of time. However, the firm stated their recollection that 12 months was specified, a priori, as the time at which efficacy would be evaluated.

From these two studies, the firm concluded that although the relapse rate was not significantly different between treatments, the time to relapse was significantly prolonged for patients receiving 6 mg budesonide QD, compared to PBO.

The firm is planning a U.S. maintenance trial, Protocol 08-3046, comparing budesonide doses of 3.0 and 6.0 mg QD to PBO over 52 weeks. Dr. Fredd noted that in the two other maintenance studies (08-3003, 08-3004), treatment did not affect the number of patients relapsing, but rather lengthened the time to relapse occurrence. He surmised that a higher dose may increase the number of patients who remain in remission. The firm proposes a primary efficacy variable of time to relapse, defined as an increase in CDAI of at least 60 units compared to baseline,

reaching a value)150, or withdrawal due to acute disease deterioration. Dr. Fredd recommended the elimination of those withdrawing as part of the efficacy variable, since disease deterioration will be captured in the CDAI.

If you have any questions concerning this IND, please contact:

Kati Johnson
Consumer Safety Officer
(301) 443-0487

8/18/95
KJ

Sincerely yours,

8/18/95

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/CSO
kj/August 18, 1995

Advice

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 21-324

Name of Drug: Entocort (budesonide) Capsules

Sponsor: AstraZeneca LP

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Combination (CRTs/CRFs provided electronically)

Submission Date: January 24, 2001

Receipt Date: January 24, 2001

Filing Date: March 24, 2001

User-fee Goal Date(s): July 24, 2001 (if priority)
November 24, 2001 (if standard, primary)
January 24, 2002 (if standard, secondary)

Proposed Indication: Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon

Other Background Information: The NDA consists of 207 archival volumes, along with the appropriate number of technical volumes

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	x		Volume 1.1 (no pagination)
2. Form FDA 356h (original signature)	x		Volume 1.1 (no pagination)
a. Establishment information	x		Volume 1.1 (no pagination)

b. Reference to DMF(s) & Other Applications	x		Volume 1.1 (no pagination)
3. User Fee FDA Form 3397	x		Volume 1.1, page 018-001-112
4. Patent information & certification	x		Volume 1.1, page 013-001-104 to 013-001-105
5. Debarment certification (Note: Must have a definitive statement)	x		Volume 1.1, page 016-001-109
6. Field Copy Certification	x		Volume 1.1, page 017-001-110
7. Financial Disclosure	x		Volume 1.1, page 019-001-115 to 019-001-215
8. Comprehensive Index	x		Volume 1.1, page 001-001-024 to 001-001-101
9. Pagination	x		Cover letter, 356h, attachments not paginated
10. Summary Volume	x		Volume 1.1
11. Review Volumes	x		Volumes 1.2 to 1.207
12. Labeling (PI, container, & carton labels)			See below
a. unannotated PI	x		Volume 1.1, page 002-001-239 to 002-001-259
b. annotated PI	x		Volume 1.2, page 003-001-010 to 003-001-029
c. immediate container	x		Volume 1.1, page 002-001-266 to 002-001-274 (provided in black and white)
d. carton	x		Volume 1.1, page 002-001-266 to 002-001-274 (provided in black and white)
e. patient package insert (PPI)	x		Volume 1.1, page 002-001-260 to 002-001-265
f. foreign labeling (English translation)	x		Volume 1.1, page 002-001-308 to 002-001-335
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		CD-ROM, Volume 1.207

14.Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		CD-ROM, Volume 1.207

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	x		Volume 1.2, page 003-001-030 to 003-001-033
2. Foreign Marketing History	x		Volume 1.2, page 003-001-033 to 003-001-036
3. Summary of Each Technical Section			See below
a. Chemistry, Manufacturing, & Controls (CMC)	x		Volume 1.2, page 003-001-037 to 003-001-056
b. Nonclinical Pharmacology/Toxicology	x		Volume 1.2, page 003-001-057 to 003-001-068
c. Human Pharmacokinetic & Bioavailability	x		Volume 1.2, page 003-001-069 to 003-001-071
d. Microbiology		x	Not applicable
e. Clinical Data & Results of Statistical Analysis	x		Volume 1.2, page 003-001-073 to 003-001-144
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	x		Volume 1.2, page 003-001-145 to 003-001-155
5. Summary of Safety		x	
6. Summary of Efficacy		x	

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	x		Volume 1.35, page 008-001-096 to 008-001-141
2. Controlled Clinical Studies			See below
a. Table of all studies	x		Volume 1.35, page 008-001-083 to 008-001-095
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		Volume 1.2, page 003-001-075 to 003-001-093 [Note: only the principal investigator is listed. Also, the table does not specify the location of the study protocols and/or study reports]
c. Optional overall summary & evaluation of data from controlled clinical studies		x	
3. Integrated Summary of Efficacy (ISE)	x		Volume 1.35, page 008-001-246 to 008-001-322
4. Integrated Summary of Safety (ISS)	x		Volume 1.36, page 008-002-017 to 008-002-279
5. Drug Abuse & Overdosage Information	x		Volume 1.36, page 008-002-280
6. Integrated Summary of Benefits & Risks of the Drug	x		Volume 1.36, page 008-002-281 to 008-002-298
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		x	

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	x		Volume 1.1, page 020-001-225 to 020-001-236
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)	x		Package insert, patient package insert provided electronically in project manager's desk copy of Volume 1.1.
a. Proposed unannotated labeling in MS WORD	x		Project Manager's desk copy of Volume 1.1
b. Stability data in SAS data set format (only if paper submission)		x	
c. Efficacy data in SAS data set format (only if paper submission)		x	
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		x	
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		x	
3. Exclusivity Statement (optional)		x	

Y=Yes (Present), N=No (Absent)

[a]□GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS□ (FEBRUARY 1987).

[b]□GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS□ (FEBRUARY 1987).

[c]□GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS□ (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

If the review team agrees, the firm will be requested to address the administrative deficiencies identified above.

_____
Name
Regulatory Health Project Manager

cc:
Original NDA
HFD-180/Div. Files
HFD-180/RPM/McNeil
HFD-180/Talarico
HFD-180/Reviewers
draft: mm/2/14/01
r/d Initials: HGallo-Torres 2/14/01
LTalarico 2/15/01
final: February 20, 2001
ADMINISTRATIVE REVIEW

APPEARS THIS WAY
ON ORIGINAL

/s/

Melodi McNeil
2/20/01 12:37:05 PM
CSO

Lilia Talarico
2/20/01 05:04:12 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM
SERVICES

DEPARTMENT OF HEALTH AND HUMAN

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: JUN 18 2001

TO: Melodi McNeil, Regulatory Project Manager
Min Lu, M.D.& A. Farrell, M.D., Clinical Reviewers
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: John Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Khairy Malek, M.D., GCP1 Reviewer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-324

APPLICANT: AstraZeneca

DRUG: Entocort CIR Capsules (budesonide CIR)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

CONSULTATION REQUEST DATE: February 9, 2001

ACTION GOAL DATE: July 24, 2001

I. BACKGROUND:

Goals of inspections: In addition to the review of the CRFs and source documents, we paid

special attention to CDAI (Crohn,s disease activity index) calculation, and inclusion criteria.

II. RESULTS (by protocol/site):

NAME (M.D.)	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
T. Winter	Cape Town	South Africa	3/1/01	6/4/01	NAI
J. Wright	Cape Town	South Africa	3/1/01	6/4/01	NAI
G. Greenberg	Toronto	Canada	3/1/01	6/4/01	VAI

A. Protocol # 08-3227

1. Site #1: Trevor Winter, M.D., Cape Town, South Africa.

We reviewed the CRFs and source documents of all 20 subjects enrolled in the study.
We did not find objectional conditions.
The data are acceptable for use in support of the NDA.

2. Site #2: John Wright, M.D., Cape Town, South Africa.

We reviewed the CRFs and source documents of all 22 subjects enrolled in the study.
The inspection did not reveal objectional conditions.
The data are acceptable for use in support of the NDA.

B. Protocol # 08-3001

1. Site # 3: Gordon Greenberg, M.D., Toronto, Ontario, Canada.

The field investigator reviewed the records of all 27 subjects enrolled. There was a minor violation observed, one subject (#629) was included in the open-label extension with a score of less than CDAI 200, as required by the protocol, at the end of the double-blind period.
This will not affect the validity of the data, which appear acceptable to be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATION:

The data appear acceptable for use in support of the NDA.

No follow-up actions are needed.

Khairy W. Malek, M.D., Ph.D.

/S/

CONCURRENCE:

/S/

John Maffin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
NDA # 21-324
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Currier
HFD-46/47/GCP 1 Chief
HFD-46/47/GCPB File # 10384, 10385, and 10386
HFD-46/47/Reading File

APPEARS THIS WAY
ON ORIGINAL

DSI CONSULT: Request for Clinical Inspections

Date: February 9, 2001

To: Malek, Khairy, GCPB Reviewer/HFD-46

Through: David A. Lepay, M.D., Ph.D., Director, DSI, HFD-45
Lilia Talarico, M.D., Director, HFD-180

From: Melodi McNeil, Regulatory Health Project Manager, HFD-180

Subject: **Request for Clinical Inspections**
NDA 21-324
AstraZeneca LP
Entocort (budesonide) Capsules

Protocol/Site Identification:

The following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon	08-3027	Dr. Trevor Winter Department of Gastroenterology Groote Schuur Hospital Observatory Cape Town 7925 South Africa
Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon	08-3027	Prof. John P. Wright Gastrointestinal Clinic Turret House Kingsbury Hospital Wilderness Road P.O. Box 44352 ZA-Clairmont, 7735 Cape Town South Africa

Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon	08-3001	Dr. Gordon Greenberg Mount Sinai Hospital Toronto, Ontario

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

__X__ There are insufficient domestic data

____ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **June 25, 2001**. We intend to issue an action letter on this application by (action goal date) **July 24, 2001**.

Should you require any additional information, please contact Melodi McNeil.

APPEARS THIS WAY
ON ORIGINAL

/s/

Melodi McNeil
2/9/01 02:20:02 PM

Lilia Talarico
2/9/01 04:50:01 PM

APPEARS THIS WAY
ON ORIGINAL

9/13/01

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 21-324 **CHEM REVIEW#:** 3 **REVIEW DATE:** September 10, 2001

SUBMISSION TYPE	DATES				
	DOCUMENT ST	CDER	ASSIGNED	REVIEW	NUM LETTER
ORIGINAL	1/24/01	1/24/01	1/30/01	5/11/01	
AMENDMENT	2/9/01	2/12/01	2/14/01	5/11/01	
AMENDMENT	4/6/01	4/9/01	4/11/01	5/11/01	
AMENDMENT	5/1/01	5/2/01	5/3/01	5/11/01	
AMENDMENT	6/18/01	6/19/01	6/19/01	7/10/01	
AMENDMENT	7/2/01	7/5/01	7/10/01	7/10/01	
AMENDMENT	7/10/01	7/10/01	7/10/01	7/10/01	
AMENDMENT	8/2/01	8/2/01	8/9/01	9/10/01	
CORRESP.	7/26/01	7/27/01	8/1/01	9/10/01	
CORRESP.	7/30/01	7/31/01	-	9/10/01	
CORRESP.	8/16/01	8/20/01	-	9/10/01	

NAME & ADDRESS OF APPLICANT: AstraZeneca LP
725 Chesterbrook Blvd.
Mailstop E3-C
Wayne, PA 19087

DRUG PRODUCT NAME:

Proprietary: Entocort EC

Nonproprietary/USAN: budesonide (USAN)

Code Name/#: S-1320

Chem.Type/Ther.Class: 3P/8015650

PHARMACOLOGICAL CATEGORY: Anti-inflammatory

INDICATION: Treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

DOSAGE FORM: Capsule

STRENGTH: 3 mg

ROUTE OF ADMINISTRATION: Oral

HOW DISPENSED: _X_ Rx ___OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See USAN

SPECIAL PRODUCT: YES_____ NO__X__

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
			Adequate	9/4/01	NA
			Adequate	8/30/01	NA
			Adequate	8/30/01	NA
			Adequate	8/30/01	NA
			Adequate	8/30/01	8/30/01
			Adequate	8/30/01	8/30/01
			Adequate	8/30/01	NA
			Adequate	8/30/01	8/30/01
			Adequate	8/30/01	NA

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

- Biopharmaceutics: complete. Recommended no references to release profile of drug in its name.
- OPDRA: complete. No issues with proposed tradename.

REMARKS/COMMENTS:

See *Summary* below.

CONCLUSIONS & RECOMMENDATIONS:

This application may be approved.

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #21-324
HFD-180/LTalarico
HFD-180/Div File/NDA #21-324
HFD-180/LZhou
HFD-180/RFrankewich
HFD-181/CSO/MMcNeil
R/D Init by: LZhou 9-10-01
RF/rpf Draft 7-6-01/**F/T 9-10-01**
C:\

**APPEARS THIS WAY
ON ORIGINAL**