CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-324

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-324

AstraZeneca LP
Attention: Barbara Blandin
725 Chesterbrook Blvd.
Mailstop E-3C
Wayne, PA 19087

Dear Ms. Blandin:

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

We acknowledge receipt of your submissions dated July 26 and 30; and August 2, 7, 8, 16, and 30, 2001. Your submission of August 2, 2001 constituted a complete response to our July 24, 2001 action letter.

This new drug application provides for the use of Entocort EC (budesonide) Capsules for the treatment of mild to moderate active Crohn's Disease involving the ileum and/or ascending colon.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and submitted draft labeling (immediate container and carton labels submitted August 2, 2001, revised to include the tradename Entocort EC). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-324." Approval of this submission by FDA is not required before the labeling is used.

We note your agreement, provided in the July 10, 2001 amendment, to continue monitoring the moisture of budesonide granules for the scale-up and product optimization batches BB1253, BB1255,

and BD1264 submitted in the NDA. Granule moisture will be monitored for both packaging configurations for each stability time point using the established test method for thermogravimetric analysis. The moisture data generated for these batches will be submitted along with updated long-term stability data and reported in the Annual Reports for this NDA.

We also refer to the August 16, 2001 teleconference in which you agreed to remove the "CIR" imprint from Entocort EC Capsules by April 23, 2002. The Division should be notified of this change in a prior approval supplement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are granting a partial waiver of the requirement for pediatric data in patients from birth up to five years of age. We are deferring submission of your pediatric studies in pediatric patients from five to 17 years of age until December 31, 2004. However, in the interim, please submit your pediatric drug development plans 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 notify you within 120 days of receipt of your response whether a waiver is granted. 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.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

Victor F.C. Raczkowski, M.D., M.S.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

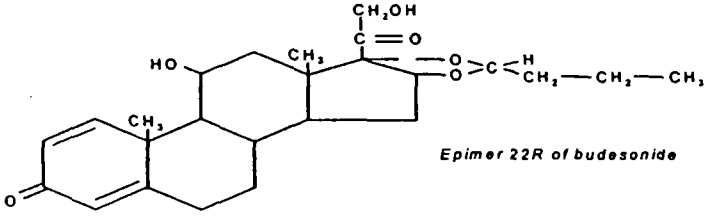
XXXXXX-XX

ENTOCORT EC™ (budesonide) CAPSULES

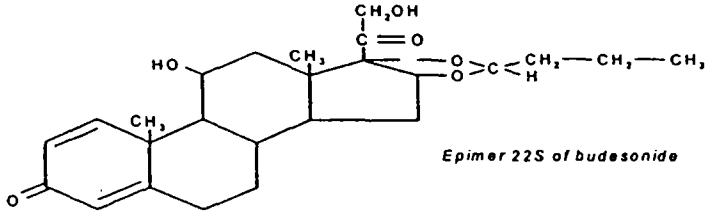
Rx only

DESCRIPTION

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



Epimer 22R of budesonide



Epimer 22S of budesonide

Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug
Administration
Rockville MD 20857

7/24/01

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:

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

We acknowledge receipt of your submissions dated February 9 and 22; March 1, March 22 and 30; April 6, 12, and 26; May 1, 24, and 30; June 4, 6, 8, 15, 18, 19, and 29; and July 2, 10, 19, 20, and 23, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert) and draft labeling (immediate container and carton labels) as described in your July 19, 2001 submission.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same

format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

We note your agreement, provided in the July 10, 2001 amendment, to continue monitoring the moisture of budesonide granules for the scale-up and product optimization batches BB1253, BB1255, and BD1264 submitted in the NDA. Granule moisture will be monitored for both packaging configurations for each stability time point using the established test method for thermogravimetric analysis. The moisture data generated for these batches will be submitted along with updated long-term stability data and reported in the Annual Reports for this NDA.

As previously noted in our May 3, 2001 letter; our July 13, 2001 facsimile; and our July 23, 2001 teleconferences, your proposed tradenames, Entocort (or alternatively Entocort XR) are not acceptable.

The drug product may not be legally marketed until you have been notified in writing that the

application is approved.

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

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

34 total pages : 15 pages + 19 pages

Draft labeling