CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-107

CHEMISTRY REVIEW(S)
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 21-107  CHEM REVIEW #2  REVIEW DATE: Nov 18, 1999

SUBMISSION TYPE
ORIGINAL
BZ Amendment
BZ Amendment
BC Amendment

DOCUMENT
Jun 29, 1999
Sep 22, 1999
Oct 25, 1999
Nov 2, 1999

DATES
CDER
Jul 1, 1999
Sep 23, 1999
Oct 27, 1999
Nov 3, 1999

ASSIGNED
Jul 6, 1999
Sep 24, 1999
Nov 1, 1999
Nov 5, 1999

REVIEW
Stability Update
Revise Draft labeling
Response to IR letter

NAME & ADDRESS OF APPLICANT:
Glaxo Wellcome Inc.
PO Box 1339 Research Triangle Park
North Carolina 27709

Contact person: Mark A. Baumgartener, R.Ph. Product Director, Regulatory Affairs
Telephone: (919) 483-3073 Fax: (919)- 483-5063

DRUG PRODUCT NAME:
Proprietary:
Nonproprietary/USAN:
Lotronex™ (alosetron hydrochloride) tablets
Alosetron Hydrochloride

Code Name/#: GR8755C
Chem.Type/Ther.Class:
Type 1/P

PHARMACOLOGICAL CATEGORY:
Serotonin 5-HT3 receptor antagonist. Antiemetic.

INDICATION:
Treatment of irritable bowel syndrome (IBS)

DOSAGE FORM:
Tablet

STRENGTH:
1 mg

ROUTE OF ADMINISTRATION:
Oral

HOW DISPENSED:
Rx

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

Structural Formula

```
                     N
                  H3
                  O
                         N
           H3  CH3  CH3
                      CH3


```

Molecular Formula

C17H18N4O.HCl

Molecular Weight

330.8

Isomerism and Stereoisomerism

Alosetron hydrochloride has no asymmetric centres and has no potential for stereoisomerism.
### SUPPORTING DOCUMENTS:

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### RELATED DOCUMENTS:

**IND**

**Patent Status:**

**Market Exclusivity:** Under Section 505(c)(3)(d)(ii) and 505(i)(4)(d)(ii) of the Federal Food, Drug and Cosmetic Act, Glaxo Wellcome requests five years of exclusivity from the date of approval of this new drug application for Alosetron Tablets for the treatment of irritable Bowel Syndrome in female patients that are diarrhea predominant as a new chemical entity pursuant to 314.108(a) and 314.108(b)(2).

**Plans for Pediatric Studies:**
Patients below the age of 18 years have not yet been included in studies with alosetron. Plans to conduct appropriate studies in pediatric patients are in the process of being finalized in consultation with a group of gastroenterology experts. A general description of Glaxo Wellcome's plans for conducting studies in pediatric patients is included in volume 1.1 page 20-25.

**Financial Disclosure:** Glaxo Wellcome has provided information required by the final rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 FR 5233) and subsequently revised by publication on December 31, 1998 (63 FR 72171)

**Certification:** In accordance with the requirements in 21 CFR § 314.50(k)(3), Glaxo Wellcome Inc. has submitted a field copy of the application that contains the technical section described under 21 CFR § 314.50 (d)(1), a copy of the application form (FDA form 356h), a copy of the application summary and a certification that the field copy of the CMC technical section is a true copy of the technical section contained in the archival and review copies of the application.

A debarment certification statement is included indicating that the company did not and will not use in any capacity, the services of any person debarred under section 306 of the FD&C Act.
CONSULTS:

Biopharm is reviewing the issues related to dissolution methods, bioavailability and formulations used in the different trials.

Trade Name: The company had submitted an amendment dated October 9, 1997 requesting the Agency concurrence with their proposed proprietary name Lotronex. This was reviewed by the Labeling and Nomenclature Committee by 02-02-98 and the Agency responded March 18, 1998 indicating no objections to the proposed proprietary name.

User Fee: NDA 21-107 has been assigned User Fee ID #

REMARKS/COMMENTS:

The BZ Amendment dated Oct 25, 1999 provided a summary of Glaxo Wellcome’s understanding of the Division’s responses to specific questions regarding the status of the NDA review. Revisions to the draft labeling related to the indication, presentation of clinical trial results and safety. Also includes additional analysis requested by the medical and statistical reviewers, information regarding three patients that developed ischemic colitis while treated with alosetron during clinical trials, information regarding unexplained rectal bleeding.

Note: The CMC issue regarding the storage statement is addressed in the response to the IR letter, question 4 of the drug product section, see below.

This Nov 2, 1999 BC amendment is a response to October 22, 1999 FDA information request.

CONCLUSIONS & RECOMMENDATIONS:

From the standpoint of CMC this application can be approved pending a satisfactory review from the Division of Biopharmaceutics and Acceptable results from the Plant Inspections.

Maria Elena Ysem, MSc
Review Chemist, HFD-180

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

cc:
NDA 21-107
HFD-180/LTalarico
HFD-180/Div File/NDA 21-107
HFD-180/LZhou
HFD-180/MYsem
HFD-181/PLEvine
D/Init by: LZhou
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA: 21-107 CHEM REVIEW #:1 REVIEW DATE: 10/7/99

SUBMISSION TYPE DATES
ORIGINAL DOCUMENT CDER ASSIGNED REVIEW
6/29/99 7/6/99
09/22/99 09/23/99 09/24/99

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North Carolina 27709

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User Fee: NDA 21-107 has been assigned User Fee ID # [redacted]

REMARKS/COMMENTS:
Because Lotronex represents a significant improvement compared to currently available treatment options for female IBS patients with diarrhea predominance, a Review Priority Classification of “P-priority Review” was requested and agreed to.

The company has indicated that all the manufacturing facilities listed in this application are inspection ready.

CONCLUSIONS & RECOMMENDATIONS:
An information request letter should be sent to the company. See review.
This application can be approved, pending the response to the Information Request letter.
A satisfactory review from the Division of Biopharmaceutics and the related DMFs and Acceptable results from the Plant Inspections.

Maria Elena Ysern, MSc
Review Chemist, HFD-180

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

cc:
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HFD-180/L.Talarico
HFD-180/Div File/NDA 21-107
HFD-180/L.Zhou
HFD-180/M.Ysern
HFD-181/P.Devine
R/D Init by: L.Zhou

APPEARS THIS WAY ON ORIGINAL