

**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:**

**Code Name/#:**

**Chem.Type/Ther.Class:**

Lotronex™(alose tron hydrochloride) tablets

Alosetron Hydrochloride

GR8755C

Type 1/P

**PHARMACOLOGICAL CATEGORY:**

**INDICATION:**

**DOSAGE FORM:**

**STRENGTH:**

**ROUTE OF ADMINISTRATION:**

**HOW DISPENSED:**

Serotonin 5-HT<sub>3</sub> receptor antagonist. Antiemetic.

Treatment of irritable bowel syndrome (IBS)

Tablet

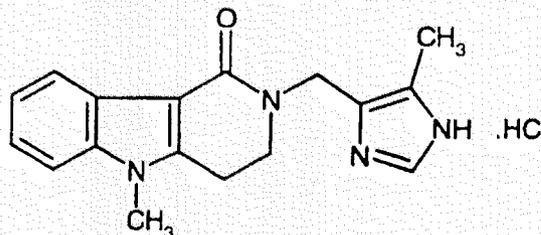
1 mg

Oral

Rx

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

**Structural Formula**



**Molecular Formula**

C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O.HCl

**Molecular Weight**

330.8

**Isomerism and Stereoisomerism**

Alosetron hydrochloride has no asymmetric centres and has no potential for stereoisomerism.

## SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
	CRC Cap		Adequate	04/27/99	----
	FoilSeal E/M-1		Adequate	03/13/96	----
	Aluminum blister		Adequate	07/30/99	
	Plant		Type I	-----	-----
	Peel Push Blister		Adequate	02/19/99	-----
	Back				
	Blue HDPE Bottle		Adequate	11/01/99	
	Marlex HHM5502		Adequate	07/29/97	
	BN				
	Blue OY-S-				
	20901		Adequate	09/21/99	
	Packaging		Type I	-----	

## RELATED DOCUMENTS:

IND [REDACTED]**Patent Status:**

The company has an U.S. Patent for Alosetron hydrochloride Tablets. The patent covers: Drug, Drug Product composition, Formulation and method of Use. The Patent Owner is Glaxo Group Limited. The U.S. Agent is Glaxo Wellcome Inc. Expiration Date for the Patent Feb 2, 2010.

**Market Exclusivity:** Under Section 505(c)(3)(d)(ii) and 505(j)(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 21CFR § 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.

/S/ 11/18/99

Maria Elena Ysern, MSc  
Review Chemist, HFD-180

/S/ 11/18/99

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/Mysern  
HFD-181/PLevine  
R/D Init by: LZhou

**APPEARS THIS WAY  
ON ORIGINAL**

LEVINE

OCT 13 1999

**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		
	DOCUMENT	CDER	ASSIGNED REVIEW
ORIGINAL	6/29/99	7/01/99	7/6/99
Amendment	09/22/99	09/23/99	09/24/99

**NAME & ADDRESS OF APPLICANT:**

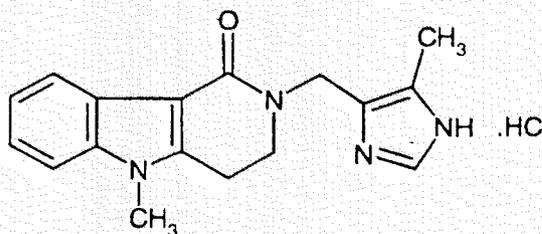
Glaxo Wellcome Inc.  
 PO Box 1339 Research Triangle Park  
 North Carolina 27709

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

**DRUG PRODUCT NAME:**

<b>Proprietary:</b>	Lotronex™ (alose tron hydrochloride) tablets
<b>Nonproprietary/USAN:</b>	Alosetron Hydrochloride
<b>Code Name/#:</b>	GR8755C
<b>Chem.Type/Ther.Class:</b>	Type 1/P

<b>PHARMACOLOGICAL CATEGORY:</b>	Serotonin 5-HT <sub>2</sub> receptor antagonist. Antiemetic.
<b>INDICATION:</b>	Treatment of irritable bowel syndrome (IBS)
<b>DOSAGE FORM:</b>	Tablet
<b>STRENGTH:</b>	1 mg
<b>ROUTE OF ADMINISTRATION:</b>	Oral
<b>HOW DISPENSED:</b>	Rx

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:****Structural Formula**

**Molecular Formula**      C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O.HCl

**Molecular Weight**      330.8

**Isomerism and Stereoisomerism**      Alosetron hydrochloride has no asymmetric centres and has no potential for stereoisomerism.

**SUPPORTING DOCUMENTS:**

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
	CRC Cap		Adequate	04/27/99	---
	FoilSeal E/M-1		Adequate	03/13/96	---
	Aluminum blister		Adequate	07/30/99	
	Plant		Type I	-----	-----
	Peel Push Blister Back		Adequate	02/19/99	-----
	Blue HDPE Bottle		Deficient		Call July, 99
	Marlex HHM5502 BN		Adequate	07/29/97	
	Blue OY-S-20901		Adequate	09/21/99	
	Packaging		Type I	-----	

**RELATED DOCUMENTS:**IND **Patent Status:**

The company has an U.S. Patent for Alosetron hydrochloride Tablets. The patent covers: Drug, Drug Product composition, Formulation and method of Use. The Patent Owner is Glaxo Group Limited. The U.S. Agent is Glaxo Wellcome Inc. Expiration Date for the Patent Feb 2, 2010.

**Market Exclusivity:** Under Section 505(c)(3)(d)(ii) and 505(j)(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 expert. 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 21CFR § 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 he 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:**

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.

/S/

10/13/99

Maria Elena Ysern, MSc  
Review Chemist, HFD-180

/S/

10/13/99

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/MYsern
- HFD-181/PDevine
- R/D Init by: LZhou

**APPEARS THIS WAY  
ON ORIGINAL**