

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 21-107/S001

Trade Name: Lotronex Tablet, 1 mg

Generic Name: alosetron hydrochloride

Sponsor: GlaxoWellcome, Inc.

Approval Date: March 7, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-107/S001

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-107/S001

APPROVAL LETTER

MAR - 7 2000

NDA 21-107/S-001

GlaxoWellcome, Inc.
Attention: Amy Mitchell
Manager, Technical Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Mitchell:

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

Name of Drug Product: Lotronex™ (alosetron hydrochloride) Tablet, 1 mg

NDA Number: 21-107

Supplement Number: S-001

Date of Supplement: February 10, 2000

Date of Receipt: February 11, 2000

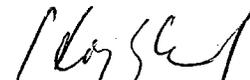
This "Changes Being Effected in 30 Days" supplemental new drug application provides for the use of _____ as an alternate primary packaging facility for the _____ container/closure system.

We have completed the review of this supplemental application and it is approved.

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 Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,



Liang Zhou, Ph.D.

Team Leader, Chemistry
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-107/S-001

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cc:

Archival NDA 21-107

HFD-180/Div. Files

HFD-180/P.Levine

HFD-180/M.Ysern

L.Zhou

HFD-095/DDMS-IMT

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: PEL-03/01/00

Initialed by: K.Johnson-03/07/00

Final: 03/08/00

Filename: supp NDA CBE30-021000 AP.doc

ACKNOWLEDGE (ACK)

APPROVAL (AP)

Handwritten: P-3/8/00
Handwritten: KJ 3/8/00

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-107/S001

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		1. Organization: HFD-180		2. NDA Number: 21-107	
3. Name and Address of Applicant (City & State): Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park North Carolina 27709-3398				4. AF Number:	
				Supplement(s)	
6. Name of Drug: Lotronex™		7. Nonproprietary Name: Alosetron Hydrochloride		Number(s) 001 CBE 30	Date(s) Feb 10, 2000
8. Supplement Provides for: Qualification of an Alternate Primary packaging Site				9. Amendments and Other (Reports, etc.) Dates: None	
10. Pharmacological Category: Serotonin receptor Antagonist. Antiemetic		11. How Dispensed: Rx		12. Related IND/NDA/DMF(s): NDA 21-107.	
13. Dosage Form: Tablet		14. Potency: 1 mg			
15. Chemical Name and Structure: See Chemistry Review #1.				6. Records and Reports:	
				Current Yes <input type="checkbox"/> No <input type="checkbox"/>	
				Reviewed Yes <input type="checkbox"/> No <input type="checkbox"/>	
17. Comments: See Review Notes. cc: NDA 21-107 HFD-180/Div File HFD-181/CSO/PLevine HFD-180/LTalarico HFD-180/MYsern R/D init by:LZhou typist:/MY/ Feb 22, 2000/ c:/word/Sup/21107001.1my					
18. Conclusions and Recommendations: This supplement can be approved.					
19. Reviewer					
Name: Maria Elena Ysern			Signature		Date Completed: Feb 2-, 2000

/ Page(s) Withheld

 / § 552(b)(4) Trade Secret /
Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-107/S001

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

FEB - 4 2000

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

DATE RECEIVED: 2/1/00

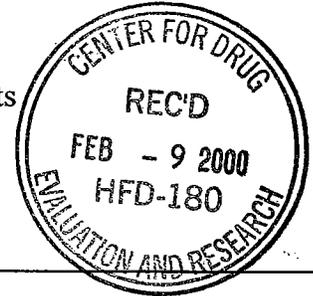
DUE DATE: 2/4/00

OPDRA CONSULT #:
00-004

TO (Division):

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

Through: Paul Levine, Project Manager
HFD-180



PRODUCT NAME:

Lotronex®
(alosetron HCl)

MANUFACTURER: GlaxoWelcome

NDA #: 21-107

Safety Evaluator: Peter Tam

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of proprietary name Lotronex®. However, OPDRA has some reservations which should be conveyed to the applicant holder. In addition, we would recommend that the firm provide us a commitment to monitor all Lotronex® postmarketing reports of medication errors or reports of potential errors.

Jerry Phillips 2/4/2000
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Peter Honig 2/4/00
Peter Honig, MD
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: 2/3/00
NDA#: 21-107
Name of Drug: Lotronex®
(alose tron HCl)
NDA Holder: GlaxoWelcome

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180) on January 10, 2000, to review the proposed proprietary drug name, Lotronex® in regard to potential name confusion with existing proprietary/generic drug names. The Division would like a decision by January 12, 2000. However, in order to render an opinion on the name, medication error staff would like more time to do a more thorough review on the proposed name. The Division comes back on 2/1/00 with a request for a definitive decision by 2/4/00.

The Labeling and Nomenclature Committee (LNC) had reviewed this proprietary name and concluded that the proposed proprietary name Lotronex® was acceptable on 11/25/99. This consult was forwarded to OPDRA for final clearance prior to approval of NDA.

PRODUCT INFORMATION

Lotronex® tablets contain 1.124 mg alose tron HCl equivalent to 1 mg of alose tron. It is indicated for the treatment of irritable bowel syndrome (IBS). The usual dose is 1 mg twice a day.

Alose tron is a potent and highly selective 5-HT₃ receptor antagonist. 5-HT₃ receptors are nonselective cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Alose tron inhibits activation of non-selective cation channels which results in the modulation of the enteric nervous system. Alose tron is rapidly absorbed after administration with a mean absolute bioavailability of approximately 50-60% (approximate range 30-90%). It is metabolized by human microsomal cytochrome P450 system and excreted

mainly through the renal route.

Lotronex® will be supplied as 1 mg tablets in bottles of 60 and 120.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, ® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (update monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online, Decision Support System (DSS), Establishment Evaluation System, and LNC database. An expert panel discussion was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process.

A. EXPERT PANEL DISCUSSION:

The panel discussed the sound-alike and look-alike names such as Lotrimin, Lotrisone, Lovenox, and Lotrel. Members of the panel voiced concern on the existing drug currently on the market by the proprietary name, Lotemax® which was approved after LNC decision was provided. Lotemax does sound and look-alike to Lotronex. The dosage form for Lotemax comes as topical ophthalmic eye drops whereas Lotronex is supplied as 1 mg oral tablets.

B. STUDY CONDUCTED BY OPDRA

Methodology:

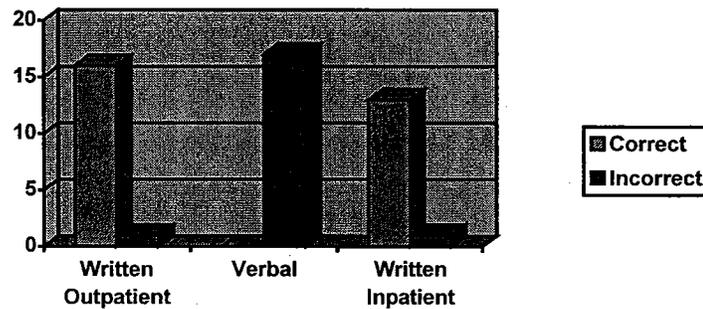
This study involved 92 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Lotronex® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff member wrote three outpatient prescriptions, each consisting of a known drug product and a prescription for Lotronex®. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions were sent to 31 participants and inpatient orders were also sent to 31 participants for review and interpretation. In addition, one pharmacist student recorded

the outpatient orders on voice mail. The voice mail messages were then sent to 30 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We understand that our sampling number is small and the study is designed to increase the likelihood of detecting failures.

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Sample</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	31	17 (55%)	16	1
Verbal	30	17 (57%)	0	17
Written Inpatient	31	14 (45%)	13	1
total	92	48 (52%)	29	19



Sixty percent of the participants responded with the correct name Lotronex®. The incorrect written and verbal responses are as follows in Table II :

Table II

	<u>Incorrectly Interpreted</u>
<u>Written</u>	Lotropex
	Voltronex
<u>Verbal</u>	<u>Phonetic Variables Responses</u>
	Voltranex
	Lotrimex
	Lotrimax (5)
	Voltramax (3)
	Fosamax*
	Lotrinex
	Ultramax (2)

	Votrimax (2)
	Loetronex

C. CONTAINER LABEL, CARTON AND INSERT LABELING:

There is no container label nor carton and insert labeling available for review from the Division.

D. CONCLUSIONS:

The results of the verbal and written analysis studies showed twenty-nine participants interpreted the proprietary name Lotronex® correctly. However, the inaccurate interpretation of the proposed name did overlap with an existing approved drug product, Fosamax® in verbal prescription study. That was not what we predicted in the expert panel discussion. Fosamax® is indicated for osteoporosis for postmenopausal women and comes in three different strengths of oral tablets; 5 mg, 10 mg, and 40 mg. Lotronex® comes as single strength of 1 mg oral tablets. Though these drug names may sound similar, they are not look-alike in written orders. Hence, OPDRA believes that the likelihood of these two names being confused, is low.

The majority of respondents provided misspelled variations of the drug name, but these responses generally were phonetic variations of the study name. These responses pose little concern since they are not proprietary names that currently marketed.

III. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name Lotronex®. However, OPDRA has some reservations which should be conveyed to the applicant holder. In addition, we would recommend that the firm provide us a commitment to monitor all Lotronex® postmarketing reports of medication errors or reports of potential errors

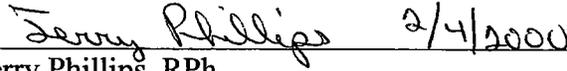
OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241



Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur



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

C.C.

NDA-21-107

Office File

HFD-180; Paul Levine, Project Manager, DGCDP

HFD-180; Lilia Talarico, Division Director, DGCDP

HFD-440; Ann Corken, Safety Evaluator, DDREII

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Deputy Director, OPDRA

HFD-002; Murray Lumpkin, Acting Director, OPDRA

GlaxoWellcome

February 10, 2000

NDA NO. 21-107 REF. NO. 001
NDA SUPPL FOR SCM CBE 30/SS

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 21-107; LOTRONEX™ (alosetron hydrochloride) Tablets
SUPAC IR: Special Supplement: Changes Being Effected in 30 Days
Qualification of an Alternate Primary Packaging Site

Dear Dr. Talarico:

Per the approval of NDA 21-107, LOTRONEX™ Tablets are currently packaged at the Glaxo Wellcome Inc. facility located in Zebulon, NC. To meet packaging demands, Glaxo Wellcome seeks qualification of _____ as an alternate primary packaging facility for the _____ container/closure system. Note that _____ is an approved secondary packaging site for LOTRONEX™ Tablets per NDA 21-107.

_____ has a satisfactory cGMP inspection status for _____ packaging operations and was last inspected by the FDA on September 16 and 17, 1999. _____ certifies that the _____ facility is in conformance with cGMPs. Furthermore, Glaxo Wellcome commits to placing the first production batch packaged at the _____ facility into the long-term stability program using the approved routine stability protocol. The stability testing will be conducted at the currently approved Glaxo Wellcome testing sites.

Per FDA Letter to NDA/ANDA Holders dated February 18, 1997, Stand Alone Packaging Operations Site Changes and Section VI.C.1.c. of Guidance for Industry: Changes to an Approved NDA or ANDA, qualification of _____ as a primary packaging facility is being submitted as a Changes Being Effected in 30 Days Supplement.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

Lilia Talarico, M.D.

February 10, 2000

Page 2

Information provided to support qualification of the alternate primary packaging site includes:

- verification that container/closure system remains unchanged
- certification from alternate packager regarding cGMP status for packaging operation
- letter of authorization to DMF
- commitment to place the first commercial batch packaged at the new site on stability using the approved routine stability protocol

The supplemental filing is provided in duplicate with one complete archival copy and one review copy. A desk copy of the supplemental filing is also being provided to Mr. Paul Levine.

Glaxo Wellcome certifies that it did not, and will not use, in any capacity, the services of any person debarred under Section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

In compliance with the requirement set forth in 21 CFR 314.50(k)(3), Glaxo Wellcome certifies that a field copy is being provided to the FDA Atlanta District.

If you have any questions or require further information, please contact Amy Mitchell at 919-483-4663.

Sincerely,



Amy Mitchell
Manager
Technical Regulatory Affairs

cc: Mr. Paul Levine (1 desk copy)

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709	3. PRODUCT NAME LOTRONEX™ (alosetron hydrochloride) Tablets
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? No 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: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER	6. LICENSE NUMBER / NDA NUMBER

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

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
<input type="checkbox"/> 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.)	<input type="checkbox"/> 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.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	
FOR BIOLOGICAL PRODUCTS ONLY	
<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> 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 side 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.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Amy Mitchell Manager Technical Regulatory Affairs	DATE February 10, 2000
--	--	---

GlaxoWellcome

February 10, 2000

Mr. Eric Weilage
Food and Drug Administration
60 Eighth Street, NE
Atlanta, GA 30309

**RE: NDA 21-107; LOTRONEX™ (alosetron hydrochloride) Tablets
SUPAC IR Changes Being Effected in 30 Days Supplement - Qualification of
an Alternate Primary Packaging Site**

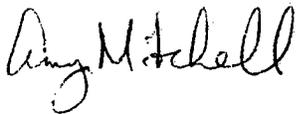
Dear Mr. Weilage:

In accordance with 21 CFR 314.50(k)(3), I am providing a Field Copy of a SUPAC IR Changes Being Effected in 30 Days Supplement. This supplemental filing qualifies as an alternate primary packaging site for LOTRONEX™ (alosetron hydrochloride) Tablets. Note that is an approved secondary packaging site for LOTRONEX™ (alosetron hydrochloride) Tablets per NDA 21-107.

I certify that the Field Copy is a true copy of the response submitted to the Division of Gastrointestinal and Coagulation Drug Products.

If you have any questions about this regulatory filing, please contact Amy Mitchell at (919) 483-4663.

Sincerely,



Amy Mitchell
Manager
Technical Regulatory Affairs

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100