CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

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NDA #: 21-228 **DATE REVIEWED:** 19-DEC-2000

REVIEW #: 1 **REVIEWER:** Michael Ortwerth

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	25-FEB-2000	28-FEB-2000	03-MAR-2000
AMENDMENT	31-MAR-2000	03-APR-2000	04-APR-2000
AMENDMENT	03-APR-2000	05-APR-2000	11-APR-2000
AMENDMENT	17-MAY-2000	18-MAY-2000	23-APR-2000
AMENDMENT	30-JUN-2000	03-JUL-2000	05-JUL-2000
AMENDMENT	03-NOV-2000	06-NOV-2000	13-NOV-2000
AMENDMENT	07-DEC-2000	08-DEC-2000	11-DEC-2000
AMENDMENT	15-DEC-2000	18-DEC-2000	19-DEC-2000

NAME & ADDRESS OF APPLICANT:

Pharmacia and Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Detrol™ LA
Established: Tolterodine tartrate
Code Name/#: Kabi 2234
PNU-200583E

Chem.Type/Rvw. Type: 3 S

PHARMACOL. CATEGORY/ PROPOSED INDICATION:

[redacted]

DOSAGE FORM: Capsule, extended release
STRENGTHS: 2mg and 4 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: X Rx __ OTC

SPECIAL PRODUCTS: __ Yes X No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

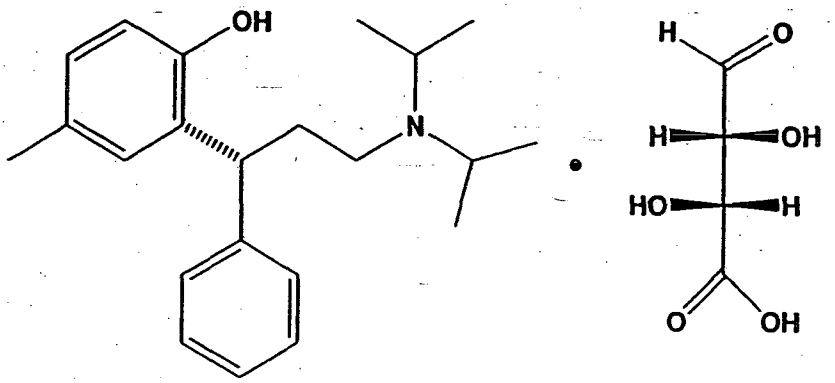
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[redacted]

Chemical Name: (R)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

Compendial Name: Tolterodine tartrate **CAS Registry Number:** 124937-52-6

Structural Formula:



Molecular Formula: $C_{26}H_{37}NO_7$ **Molecular Weight:** [redacted]

SUPPORTING DOCUMENTS:

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
[redacted]			[Adequate]	15-SEP-2000 AShaw	NA
[redacted]			[Adequate]	23-APR-1998 AAl-Hakim	NA
[redacted]			[Adequate]	20-MAR-1999 HKhorshidi 16-FEB-2000 KSwiss	NA
[redacted]			[Adequate]	16-NOV-2000 MOrtwerth	NA
[redacted]			[Adequate]	12-MAY-1999 RHarapanhalli	NA
[redacted]			[Adequate]	16-NOV-2000 MOrtwerth	NA

Type/ Number	Subject	Holder	Status	Review Date	Letter Date
			[Adequate]	10-SEP-1999 SZuk	NA
			[Adequate]	22-FEB-1999 RFrankewich	NA
			[Adequate]	01-SEP-1999 JVidra	NA
			[Adequate]	06-DEC-2000 MOrtwerth	NA
			[Adequate]	06-MAR-2000 GGill-Sangha	NA
			[Adequate]	13-AUG-1999 JVidra	NA
			[Adequate]	28-JUL-1999 JVidra	NA

RELATED DOCUMENTS (if applicable): NA

CONSULTS:

Due to Agency policy on Tradename review, a consult was sent to the Office of Post-Marketing Drug Risk Assessment (OPDRA) on [18-JUL-2000]. A Consultation Response (see Attachment 1) from OPDRA dated [28-SEP-2000] was received which gave the following recommendation:

> "OPDRA does not recommend the use of the modifier, [redacted], for tolterodine extended-release capsules. However, the use of the alternate modifier, "LA", is not objectionable."

Since this review decision was made for an NDA with an action date within 90 days of the OPDRA review, OPDRA considers this their final review.

An Establishment Evaluation Request was submitted on 05-APR-2000 to the Office of Compliance and an overall recommendation of ACCEPTABLE for the drug substance and drug product manufacturing and packaging facilities was provided on 07-DEC-2000. (See Attachment 3).

REMARKS:

The drug product manufacturer is International Processing Corporation in Winchester, Kentucky. The primary drug product packaging facility is Pharmacia and Upjohn Company in Kalamazoo, Michigan and the secondary packager is [redacted]. Pharmacia and Upjohn in Kalamazoo, Michigan will also function as an alternate control operations facility for the drug product.

In the submission dated 17-MAY-2000, the sponsor requested concurrence on a District Office [redacted]

[redacted]

District Office decision to be acceptable.

Through the approval of NDA 20-771, Tolterodine tartrate is marketed as an immediate release product in 1mg and 2 mg doses by the sponsor. The submission of this application (NDA 21-228) is for a new extended release dosage form for the treatment of patients with overactive bladder with [redacted]

The drug product proposed for marketing is to be manufactured in a capsule formulation. As of the date of this review, 12 primary and 3 supportive stability lots have been provided for the drug product capsules in multiple packaging configurations (foil blisters and HDPE bottles). In the case of primary stability lots, 9 months of stability data is provided for 25°C/60%RH and 30°C/60%RH storage conditions and 6 months of data is provided for the 40°C/75%RH storage condition. For the supportive stability data, 18 months of stability data is provided for 25°C/60%RH and 30°C/60%RH storage conditions and 6 months of data is provided for the 40°C/75%RH storage condition.

Amendment Submissions:

Document Date	Submission Contents
31-MAR-2000	This is a revised edition of Item 4 (CMC) Vol. 2 to replace the original submission volume 2, which was missing figures on pages 30-66.
03-APR-2000	As requested by the chemistry reviewer, this is the sponsor's listing of all facilities for the NDA as well as a statement that all facilities are ready for inspection.
17-MAY-2000	This is a Manufacturing Process Development proposal sent to the FDA supervisory investigator at the Cincinnati District Office. The submission was sent to the reviewing chemist for concurrence on the District Office recommendation.
30-JUN-2000	This amendment includes a stability update for Tolterodine tartrate drug product, a encapsulation equipment addition, and a new testing facility for excipients.
03-NOV-2000	This is a letter of authorization to cross reference supplement submission SCM-003 for NDA 20-771. SCM-003 is a prior approval supplement for the synthesis of Tolterodine tartrate via manufacturing process B which was approved on 25-MAY-2000.
07-DEC-2000	This submission is in response to the CMC IR letter dated 22-NOV-2000 sent to the sponsor.
15-DEC-2000	This is the sponsor's response to final requests for changes in labeling, which included the [redacted]

CONCLUSIONS & RECOMMENDATIONS:

From a Chemistry, Manufacturing, and Controls perspective, this NDA may be **APPROVED.**

/S/
Michael Ortwerth, Ph.D.
Review Chemist, HFD-580

19-DEC-2000
Date

/S/
Moo-Jhong Rhee, Ph.D.
ChemistryTeam Leader, HFD-580

12-19-2000
Date

cc:
Org. NDA 21-228
HFD-580/Division File
HFD-580/MOrtwerth
HFD-580/CSO/EFarinas
HFD-580/MRhee
R/D Init by: MRhee

filename: N21228.001.doc

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE

70 pages

ATTACHMENT 3

EER Detail Report

08-DEC-2000 FDA CDER EES Page 1 of 4
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21228/000
Stamp: 28-FEB-2000
Regulatory Due: 28-DEC-2000
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE ROAD
KALAMAZOO, MI 49001
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 29-OCT-2000
Brand Name: [redacted] 2/4MG CAPS
Estab. Name:
Generic Name: TOLTERODINE [redacted] 2/4MG CAPS
Dosage Form: (EXTENDED RELEASE CAPSULE)
Strength: 2MG AND 4MG

Application Comment: THE SPONSOR PROPOSES THEIR EXTENDED RELEASE CAPSULES FOR THE [redacted]

FDA Contacts: E. FARINAS (HFD-580) 301-827-4260 , Project Manager
M. ORTWERTH , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 07-DEC-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities: [redacted]
Profile: CTR OAI Status: NONE
Estab. Comment: [redacted] (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
OC RECOMMENDATION	05-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 1528607
INTERNATIONAL PROCESSING CORP
1100 ENTERPRISE DR
WINCHESTER, KY 403919668
DMF No: [redacted] AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CTR OAI Status: NONE
Estab. Comment: MANUFACTURE AND QUALITY CONTROL OF BEADS. ENCAPSULATION, QUALITY CONTROL, RELEASE TESTING, AND STABILITY TESTING OF THE DRUG PRODUCT. (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
SUBMITTED TO DO	05-APR-2000	10D			DAMBROGIOJ
ASSIGNED INSPECTION	07-SEP-2000	PS			SEASTHAM
ASSIGNED INSPECTION	12-SEP-2000	PS			SEASTHAM
ASSIGNED INSPECTION	12-SEP-2000	PS			SEASTHAM
ASSIGNED INSPECTION	12-SEP-2000	PS			SEASTHAM
ASSIGNED INSPECTION	12-SEP-2000	PS			SEASTHAM

DO RECOMMENDATION	25-OCT-2000	ACCEPTABLE INSPECTION	SEASTHAM

AN ON-SITE PRE-APPROVAL INSPECTION WAS PERFORMED 10/17-19/00. NO OBJECTIONABLE CONDITIONS WERE NOTED AND FIRM IS CAPABLE OF MANUFACTURING AND TESTING THE PRODUCT.

OC RECOMMENDATION	30-OCT-2000	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

[redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CTL OAI Status: NONE
Estab. Comment: [redacted]

[redacted]

[redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	17-OCT-2000				RHEEM
OC RECOMMENDATION	17-OCT-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: [redacted]

[redacted]

DMF No: AADA:
Responsibilities:

[redacted]

Profile: CSN OAI Status: NONE
Estab. Comment:

[redacted]

by M. ORTWERTH ( )

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
SUBMITTED TO DO	05-APR-2000	GMP			EGASM
ASSIGNED INSPECTION	07-APR-2000	GMP			EGASM
INSPECTION SCHEDULED	16-AUG-2000		26-SEP-2000		IRIVERA
INSPECTION PERFORMED	12-OCT-2000		27-SEP-2000		EGASM
DO RECOMMENDATION	07-DEC-2000			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	07-DEC-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 2650013
PHARMACIA AND UPJOHN CARIBE INC
HIGHWAY 2 KM 60.0
BARCELONETA/ARECIBO, PR 00617
DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: MANUFACTURE (STEP 4 AND MILLING), QUALITY CONTROL, RELEASE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE B-PROCESSING DRUG SUBSTANCE (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
OC RECOMMENDATION	05-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: 1810189
PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: DS OPERATIONS: MANUFACTURE (STEPS 1-3, ALTERNATE FOR STEP 4), QUALITY CONTROL, RELEASE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE B-PROCESS DRUG SUBSTANCE.
DP OPERATIONS: PRIMARY PACKAGING, LABELING, QUALITY CONTROL, AND FINAL RELEASE OF THE DRUG PRODUCT. ALTERNATE FOR CAPSULE RELEASE AND STABILITY TESTING. (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
OC RECOMMENDATION	05-APR-2000			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	07-APR-2000				ORTWERTHM
OC RECOMMENDATION	07-APR-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 9610190
PHARMACIA AND UPJOHN SPA
MARINO DEL TRONTO, ASCOLI PICENO, IT

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: QUALITY CONTROL, RELEASE, STORAGE, AND STABILITY TESTING OF TOLTERODINE L-TARTRATE A-PROCESS DRUG SUBSTANCE. (on 05-APR-2000 by M. ORTWERTH ())

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-APR-2000				ORTWERTHM
SUBMITTED TO DO	05-APR-2000	10D			EGASM

ASSIGNED INSPECTION	07-APR-2000 GMP			EGASM
INSPECTION SCHEDULED	12-SEP-2000	13-OCT-2000		IRIVERA
INSPECTION PERFORMED	16-OCT-2000	13-OCT-2000		EGASM
DO RECOMMENDATION	07-DEC-2000		ACCEPTABLE	EGASM
			INSPECTION	
OC RECOMMENDATION	07-DEC-2000		ACCEPTABLE	EGASM
			DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

Statistics review(s) and memoranda regarding dissolution and/or stability

Not applicable for this submission.

Number of Pages Redacted 3

❖❖❖

Confidential,
Commercial Information

Memorandum to the File

To: NDA 21-228
From: Michael Ortwerth, Ph.D.; Review Chemist MO. 12-21-00
Amit Mitra, Ph.D.; Acting Chemistry Team Leader /S/ 12-21-00
Re: OPDRA Labeling Consult Dated 10/02/00: Consult #: 00-0190
Date: 21-DEC-2000

Comments:

This memorandum is in reference to the OPDRA consult (# 00-0190) dated 10/02/00 in which OPDRA made recommendations on the sponsor's drug product primary and secondary packaging labeling as well as on the appearance of the drug product itself. The consult comments are deemed by this reviewer to be not in relationship to the product under review.

For example:

OPDRA STATEMENTS:
"The blisters contain — tablets with an empty square in the middle of the pack"

"Although the —— strengths..."

REVIEWER COMMENTS:

The blisters do not contain — tablets. The blisters contain 10 capsules.

The drug product is manufactured in 2mg and 4mg doses not —— doses.

Finally, the sponsor submitted information concerning drug product primary and secondary packaging to their application in their amendment submissions dated 07-DEC-2000 and 15-DEC-2000. The mock-up printed labeling was reviewed by this reviewer in CMC review #1 dated 19-DEC-2000 and deemed satisfactory.

Thus, the comments made by OPDRA reviewers in OPDRA consult # 00-0190 concerning primary and secondary drug product packaging and the to-be-manufactured drug product dosage form for NDA 21-228 are found not applicable and are superceded by the review results of the sponsor's amendment submissions dated 07-DEC-2000 and 15-DEC-2000.

SPECIAL NOTE: This memorandum DOES NOT invalidate OPDRA's review of the drug product tradename.

Conclusion:

It is therefore determined that the CMC information provided for drug product mock-up labeling in the sponsor's amendment submissions dated 07-DEC-2000 and 15-DEC-2000 is adequate to support NDA 21-228. The filing of this memorandum was given verbal concurrence from the project manager for NDA 21-228 and the Deputy Director for HFD-580.

The status of the sponsors application, as stated in CMC Review #1 dated 19-DEC-2000, remains 'APPROVED' from a Chemistry, Manufacturing, and Controls perspective.

cc: HFD-580/Division File (NDA 21-228)
HFD-580/MOrtwerth/MRhee
HFD-580/PM-CSO/EFarinas