Number of Pages Redacted 1

Confidential,
Commercial Information

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

March 21, 2000

Ms. Evelyn Farinas,
Division of Reproductive and Urologic
Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17-B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-228
Tolterodine — release capsules

General Correspondence: Desk Copies

Dear Ms. Farinas:

Reference is made to your March 10 request for electronic copies of the CMC and Pharmacology sections of the above NDA. Enclosed please find compact discs containing Item 4 and Item 6.

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Jim Chaber FOR

Gregory G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS:mlw

Attachment

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

March 31, 2000

DUPLICATE

Division of Reproductive Health and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-228
Tolterodine [redacted] release capsules

Amendment #1

Dear Sir/Madam:

NC

It has come to our attention that several figures in Volume 2 of Item 4 (Overall volume 1.3 of 1.51) did not print from the electronic publisher used to produce the above NDA. Enclosed please find a replacement volume which now includes the missing figures. Pages 30-66 are replaced in this revised volume. No content has been changed except to add the figures that did not print in the original publication.

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS/crdt

Enclosures

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

Pharmacia&Upjohn

February 25, 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Ave.
Rockville, MD 20857

RE: NDA 21-228
Tolterodine — release capsules

Original Submission of New Drug Application

Dear Sir/Madam:

Under the provisions of 21 CFR 314.50, Pharmacia & Upjohn is a submitting a New Drug Application, NDA 21-228, for tolterodine — release capsules (trademark yet to be decided). This application supports the product being indicated for the treatment of patients with an overactive bladder and symptoms of urinary frequency, urgency or urge incontinence.

Tolterodine — release capsules were evaluated in seven clinical trials enrolling 1659 patients. This submission includes safety data for over 400 patients treated for at least 6 months.

Format and content of this NDA has been discussed with the Division on November 3, 1999. At that time it was agreed that Items 11 and 12 would be submitted electronically.

Only an electronic archival copy of Items 11 and 12 is being submitted. They are provided on 1 ISO 9660 CD in PDF format and organized according to FDA's Guidance for Industry, Archiving Submissions in Electronic Format—NDA's, January 1999. The total size of the electronic parts is 471 megabytes (56 MB for Item 11 and 415 MB for Item 12) and have been scanned with Network Associates's McAfee Virus Scan Software for Windows version 4.03. All electronic information is contained in the directory N21228 and a copy of this letter and the 356H form are also provided as PDF files (cover.pdf and 356H.pdf respectively) in this directory.

Attachment 1 contains an abbreviated table of contents (TOC) for the NDA and is also provided as a PDF file (ndatoc.pdf) in directory N21228. The abbreviated NDA TOC provides hyperlinked connections to tables of contents for Case Report Tabulations and Case Report Forms. The table of contents are then either bookmarked or hyperlinked to individual profiles or CRF's.

Items 1, 2, 3, 11, 12, 13, 14,16,17,18 and 19 are contained in volume 1.1 of the submission. Additional copies of this volume are provided with review copies for Items 4, 5, 6, 8 and 10. An additional 20 desk copies of this volume have been sent to Evelyn Farinas's attention.

A user fee check made payable to the Food and Drug administration in the amount of — was sent to the Mellon Bank, Pittsburgh, PA. on February 25, 2000.

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS:mlw

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-228

INFORMATION REQUEST LETTER

Pharmacia & Upjohn Company
Attention: Gregory Shawaryn
Regulatory Manager, U.S. Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tolterodine extended release capsules.

We also refer to your submission dated February 25, 2000.

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submissions and have the following comment.

The proposed IVIVC analysis is currently under review and any comments and recommendations regarding its acceptability will be forwarded to you at a future time.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827

Sincerely,

Daniel Shames, M.D
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-228

INFORMATION REQUEST LETTER

Pharmacia & Upjohn
Attention: Gregory Shawaryn
Regulatory Manager
7000 Portage Road
Kalamazoo, MI

Dear Mr. Shawaryn:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tolterodine extended release capsule, 2 mg and 4 mg.

We also refer to your submissions dated March 31, April 03, May 17, June 30 and November 03, 2000.

We are reviewing the Chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide detailed, quantitative sampling procedures for the [redacted] and finished drug product batches. These procedures should support adequate representation of the entire respective batches.

2. An expiry period of [redacted] is unacceptable for the drug product. Available real-time data are adequate to support the granting of 18 months of expiration dating for the drug product.

3. Please submit an amended post-approval stability commitment stating that:

   "The first three full-scale commercial production lots for all capsule strengths will be included in the post-approval stability protocol and extension of expiration dating will be based on [redacted] from three commercial production batches."

4. Please update your Methods Validation Package to contain all of the following information and resubmit the updated Methods Validation Package in triplicate:
   a.) A list of samples for verification/validation including quantity of samples to be provided and control numbers for the lots to be submitted,
   b.) Test results obtained for the submitted samples (Alternatively, COAs may be supplied for the aforementioned lots.),
   c.) The qualitative and quantitative composition of the drug product,
   d.) Specifications for the drug product,
   e.) The regulatory methods,
   f.) Methods validation data supporting accuracy, selectivity, specificity, etc., and
   g.) Material Safety Data Sheets (MSDSs) for the active pharmaceutical ingredient.

5. Concerning drug product labeling:

a.) The Header on the first page of the Physicians Insert labeling reads ' capsules". In this statement ' should be replaced with the drug product tradename while the phrase ' should be rewritten to read "extended-release capsules".

b.) The Physicians Insert labeling should include the tradename of the drug product in the appropriate sections where the term ' is currently in place.

c.) In the DESCRIPTION section of the Physicians Insert labeling, it is stated that "The inactive ingredients include ethylcellulose, gelatin, hydroxypropyl methylcellulose, starch, sucrose and This statement should be replaced with a statement that includes all drug product inactive ingredients.

d.) In the HOW SUPPLIED section of the Physicians Insert labeling the following changes should be included.

i) A statement

ii) Complete NDC numbers for the 2 and 4 mg container closure systems should be provided.

iii) The manufacturing statement should be replaced to read:

"Manufactured for Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA
By
International Processing Corporation
Winchester, Kentucky 40391, USA"

e.) Mock-up labeling should be provided for all primary and secondary drug product packaging (i.e., cartons, packages, bottle labels, etc.).

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, Division of
Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

D/f

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-228

Pharmacia Upjohn
Attention: Gregory Shawaryn
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

MAY - 1 2000

Dear Mr. Shawaryn:

We acknowledge receipt on April 14, 2000 of your April 12, 2000, correspondence requesting a pediatric exclusivity meeting of your drug tolterodine. FDA categorizes meetings into three types:

Type A: A meeting that is necessary for an otherwise stalled drug development program to proceed.
Type B: A meeting described under drug regulations (e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2/Pre-Phase 3, Pre NDA).
Type C: All meetings other than those that qualify for Type A or B.

Your correspondence indicated this to be a Type A meeting and we concur. This meeting has been scheduled for:

Date:	May 15, 2000
Time:	11:30 am
Location:	Telephone Conference Call
CDER participants:	Drs. Allen, Mann, Shames, Gierhart, Parekh, Chatterjee, Raczkowski, Ms. Farinas and Rumble

The background information for this meeting should be received by the Agency at least two weeks prior to the meeting. If we do not receive it by May 1, 2000, rescheduling of the meeting may be necessary.

If you have any questions, contact Evelyn Farinas, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 4/28/00

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
HFD-580/ NDA 21-228
HFD-580/Div. Files
HFD-580/ Farinas
Drafted by: Olmstead/April 18, 2000
Initialed by: Rumble 4.25.00
final: olmstead 4.26.00
filename: PU5-15-00CL.doc

GENERAL CORRESPONDENCE (MEETING TYPE)

Farinas

NDA 21-228

MAR - 1 2000

Pharmacia & Upjohn
Attention: Gregory G. Shawaryn
Regulatory Manager, U.S. Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

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

Name of Drug Product:	tolterodine [redacted]elease capsules, 2 and 4 mg capsules
Therapeutic Classification:	Standard (S)
Date of Application:	February 25, 2000
Date of Receipt:	February 28, 2000
Our Reference Number:	NDA 21-228

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 28, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 28, 2000 and the secondary user fee goal date will be February 28, 2001.

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development 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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. 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.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Evelyn Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 3/1/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-228
HFD-580/Div. Files
HFD-580/EFarinas
HFD-580/Allen/Mann/Shames/Jordan/Parekh/Rhee/Rumble

DISTRICT OFFICE

Drafted by: erf/March 1, 2000
Initialed by: Rumble 03.01.00
final: erf/03.01.00
filename:

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

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

2 pages

Number of Pages Redacted 14

Draft Labeling
(not releasable)

Teleconference Minutes

Date: December 13, 2000 **Time:** 4:00 pm **Location:** Parklawn; 17B-45

NDA 21-228 **Drug:** tolterodine extended release capsules

Indication: overactive bladder

Sponsor: Pharmacia & Upjohn

Type of Meeting: Guidance

Meeting Chair: Terri Rumble, Chief, Project Management Staff, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participants: Greg Shawaryn, Regulatory Manager, Pharmacia & Upjohn
Mark Mondabach, Regulatory Affairs, Pharmacia & Upjohn

Meeting Recorder: Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)

Meeting Objective: To provide sponsor feedback regarding tradenames proposed for this NDA.

Background:

- Proposed tradename, Detrol LA, was found to be acceptable by OPDRA and DRUDP
- Proposed tradename, ——, was found to be unacceptable by OPDRA and DRUDP
- Sponsor submitted new tradename, ——, for consideration by OPDRA and DRUDP

Discussion:

- Sponsor was informed that tradename, —— is not acceptable from the Division's perspective; there are similar concerns with regard to potential medication errors for a product with this tradename as were identified for ——
- The NDA cannot be approved at this time without resolution of either an acceptable tradename or withdrawal of the unacceptable tradenames from the NDA
- Sponsor's options were discussed, which include the following:
  - Keep Detrol LA and proceed with negotiations for approval of NDA, and withdrawing —— and —— from the NDA application; a subsequent Labeling Supplement could be submitted for review but no PDUFA goal would be in effect for action on this labeling supplement
  - Withdraw all tradenames from the NDA and proceed with negotiations for approval of the NDA; a subsequent Labeling Supplement could be submitted for review but no PDUFA goal would be in effect for action on this labeling supplement
  - Not withdraw any tradenames from the NDA, which would be an approvability issue for this pending NDA; a response to the approvable letter might only involve submission of labeling (with acceptable tradename for review, or no tradename to consider) for review and a Safety Update, and this resubmission would be on a 2-month PDUFA review clock

Decisions made:

- Sponsor will consider these options and inform DRUDP of their decision for this pending NDA

Unresolved decisions: none

Action Items:

- Provide a copy of these teleconference minutes to the sponsor within 30 days
- Pharmacia & Upjohn to inform DRUDP of decision regarding tradename and labeling

Lead and Minutes Preparer

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 22-228
HFD-580/DivFile
HFD-580/PM/Rumble/Farinas
HFD-580/shames/rhee/ortwerth/

drafted: Rumble/12.13.00/21228tcon.doc
final: Rumblet, 12.18.00

TELECONFERENCE MINUTES

APPEARS THIS WAY
ON ORIGINAL

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

13 pages

Appendix 1

NDA 21-228

INFORMATION REQUEST LETTER

Pharmacia & Upjohn
Attention: Gregory Shawaryn
Regulatory Manager
7000 Portage Road
Kalamazoo, MI

Dear Mr. Shawaryn:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tolterodine extended release capsule, 2 mg and 4 mg.

We also refer to your submissions dated March 31, April 03, May 17, June 30 and November 03, 2000.

We are reviewing the Chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide detailed, quantitative sampling procedures for the bead batches and finished drug product batches. These procedures should support adequate representation of the entire respective batches.

2. An expiry period of [redacted] is unacceptable for the drug product. Available real-time data are adequate to support the granting of 18 months of expiration dating for the drug product.

3. Please submit an amended post-approval stability commitment stating that:

"The first [redacted] lots for all capsule strengths will be included in the post-approval stability protocol and extension of expiration dating will be based on real-time data from [redacted] batches."

4. Please update your Methods Validation Package to contain all of the following information and resubmit the updated Methods Validation Package in triplicate:
   a.) A list of samples for verification/validation including quantity of samples to be provided and control numbers for the lots to be submitted,
   b.) Test results obtained for the submitted samples (Alternatively, COAs may be supplied for the aforementioned lots.),
   c.) The qualitative and quantitative composition of the drug product,
   d.) Specifications for the drug product,
   e.) The regulatory methods,
   f.) Methods validation data supporting accuracy, selectivity, specificity, etc., and
   g.) Material Safety Data Sheets (MSDSs) for the active pharmaceutical ingredient.

5. Concerning drug product labeling:

a.) The Header on the first page of the Physicians Insert labeling reads " In this statement ' should be replaced with the drug product tradename while the phrase " " should be rewritten to read "extended-release capsules".

b.) The Physicians Insert labeling should include the tradename of the drug product in the appropriate sections where the term " is currently in place.

c.) In the DESCRIPTION section of the Physicians Insert labeling, it is stated that "The inactive ingredients include ethylcellulose, gelatin, hydroxypropyl methylcellulose, starch, sucrose and This statement should be replaced with a statement that includes all drug product inactive ingredients.

d.) In the HOW SUPPLIED section of the Physicians Insert labeling the following changes should be included.

i) A statement should be

ii) Complete NDC numbers for the 2 and 4 mg container closure systems should be provided.

iii) The manufacturing statement should be replaced to read:

"Manufactured for Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA
By
International Processing Corporation
Winchester, Kentucky 40391, USA"

e.) Mock-up labeling should be provided for all primary and secondary drug product packaging (i.e., cartons, packages, bottle labels, etc.).

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, Division of
Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Status Meeting Minutes

Date: November 9, 2000 **Time:** 1:00-1:25 PM, EST **Location:** Parklawn; 17B43

NDA 21-228 **Drug:** tolterodine extended release **Indication:** [redacted]

Sponsor: Pharmacia & Upjohn Corporation

Type of Meeting: Status

Meeting Chair: Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Michael Ortwerth, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
D. J. Chatterjee, Ph.D. –Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Barbara Chong – Consumer Safety Officer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss review status of NDA 21-228.

Background: Goal date is December 28, 2000.

Discussion:

- Clinical: "Detrol LA" is the preferred trademark; revised package insert should list all inactive ingredients (in line 20), include biopharmaceutic comments recommended by Dr. Chatterjee, describe clinical studies as in the Detrol immediate release package insert, delete graphics, and include QT information in the Adverse Events section
- Biopharmaceutics: comments incorporated into the N:drive package insert
- Chemistry: OPDRA trademark review will be attached to the Chemistry review
- DDMAC: recommend clarification of the language in lines 12 through 19 of the sponsor's proposed package insert to conform to the language already present in the Detrol immediate release package insert
- desired date for completion of reviews and submission of Action Package to Dr. Shames is December 12, 2000

Action Items:

- the word '—— will be deleted in DRUDP's proposed package insert
- send revised DRUDP's patient insert for NDA 21-228 to the sponsor during the week of November 20, 2000 (*faxed to sponsor on November 27, 2000*
- statistician to review the N:drive tolterodine extended release patient insert and submit his review

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
IND Arch:
HFD-580/DivFile

HFD-580/Allen/Shames/Gierhart/Batra/Rhee/Ortwerth/Jordan/McLeod/Parekh/Chatterjee/Rumble/Farinas
HFD – 42/Chong

drafted: Farinas, 11.28.00
concurrence: Shames 11.29.00/Gierhart 11.30.00/Batra/Ortwerth 11.30.00/ Rumble 11.29.00
final: Farinas, 12.11.00

filename: ——
MEETING MINUTES

Status/Labeling Meeting Minutes

Date: October 23, 2000 **Time:** 10:30-11:30 AM, EST **Location:** PKLN; 17B43

NDA 21-228 **Drug:** tolterodine extended release **Indication:** [redacted]

Sponsor: Pharmacia & Upjohn Corporation

Type of Meeting: Status/labeling meeting

Meeting Chair: Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager

FDA Attendees:
Daniel Shames, M.D. – Medical Team Leader, DRUDP (HFD-580)
Brenda Gierhart, M.D. - Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)
Michael Ortwerth, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Laurie McLeod, Ph.D. – Pharmacologist, DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To provide update on the review status of this NDA.

Background: On February 28, 2000, DRUDP received NDA 21-228 for tolterodine [redacted] release from Pharmacia & Upjohn Company. The sponsor is seeking approval of this product for the treatment of patients with overactive bladder with symptoms of frequency, urgency and/or urge incontinence. Two clinical protocols (98-TOCR-007 and 98-TOCR-008) and six biopharmaceutics studies (97-TOCR-001, 97-TOCR-002, 97-TOCR-003, 98-TOCR-005, 98-TOCR-006 and 98-TOCR-010) were submitted for review. The primary goal date for this NDA is December 28, 2000.

Discussion:
- Biopharmaceutics:
  - projected completion of review by second week in November
- Pharmacology/Toxicology:
  - Drs. McLeod and Jordan will review the proposed label
  - it will be verified that the anesthetized cat data should be removed from the proposed label, as recommended by DDMAC
- Chemistry:
  - Chemistry reviewer previously recommended to OPDRA that this product be addressed as "extended release" and not ' [redacted] "; OPDRA recommends adoption of Detrol LA as the tradename for this product, instead of the sponsor's preferred tradename [redacted]

- facilities inspections in the US are adequate; two foreign facilities were given 483's (waiting for list of deficiencies)
- stability data: difficult to agree with sponsor's request for [redacted] since stability data for the primary lot is available for nine months only
- release profile needs Biopharmaceutics review

- Clinical:
  - trademark consult: OPDRA indicated preference for the Detrol LA tradename citing safety concerns due to potential pharmacy dispensing confusion between Ditropan XL
  - clinical review of additional studies submitted June 28, 2000, is ongoing
  - pediatrics: [redacted]

- Statistics:
  - statistical data provided appears adequate
  - rationale for including data from previous trials in the labeling is questionable and may be confusing to practitioners
- Future plans:
  - aim for providing revised label comments to sponsor in three weeks
  - aim to make label revisions on the N-drive posted label; limit meeting discussions only to discrepancies
  - aim for completion of NDA's primary reviews by December 12
  - aim for final action on December 22, 2000

Action Items:

- [redacted]
- reviewers will make label revisions in the N-drive label
- revised label to be sent to sponsor in three weeks from this meeting (i.e., mid-November)
- Project Manager will set up two meetings, the first one in three weeks to discuss the label revisions to be sent to the sponsor, and the second in five weeks to discuss the sponsor's reply to DRUDP's label revisions
- Project Manager to contact DDMAC reviewer, Barbara Chong, for her input into the label revisions

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
IND Arch:
HFD-580/DivFile
HFD-580/
Allen/Shames/Gierhart/Batra/Parekh/Chatterjee/Ortwerth/Rhee/Jordan/McLeod/Hoberman/Kammerman/Rumble
drafted: Farinas, 10.24.00

concurrence: Shames 10.24.00/Gierhart 10.25.00/Batra/Hoberman/Ortwerth 10.25.00/Chatterjee 10.25.00/McLeod/KC for TR 10.27.00
final: Farinas, 11.30.00

MEETING MINUTES

D/1

Meeting Minutes

Date: August 24, 2000 **Time:** 1:00-1:30 **Location:** PKLN; 17 B45

NDA 21-228 **Drug:** tolterodine release **Indication:**

Sponsor: Pharmacia & Upjohn Company

Type of Meeting: Status

Meeting Chair: Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager

FDA Attendees:
Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. - Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager

Meeting Objective: To provide update on the review status of this NDA.

Background: On February 28, 2000, DRUDP received NDA 21-228 for tolterodine release from Pharmacia & Upjohn Company. The sponsor is seeking approval of this product for the Only one protocol (98-TOCR-007) was submitted for review. The primary goal date for this NDA is December 28, 2000.

Discussion:
- Chemistry: under review; no issues to discuss (per Chemistry reviewer, M. Ortwerth)
- Pharmacology/Toxicology: under review; no issues to discuss (per Pharm/Tox reviewer, L. McLeod)
- Biopharmaceutics: under review
- Statistics: under review
- Clinical:
  - review of Protocol 98-TOCR-007 in NDA 21-228 submission of February 28, 2000, indicated that Protocol Amendment 4 had not been submitted to previously, and thus was not reviewed; of concern is that Protocol Amendment 4 proposes "estimation" of values; the statistical analysis proposed will have an effect on NDA 21-228 and NDA 20-771 (immediate release tolterodine)
  - sponsor did not pre-specify a clinically meaningful difference in weekly incontinence episodes of treatment versus placebo

Action Items:

- Protocol Amendment 4 will be reviewed and discussed at next status meeting
- the sponsor's proposed label included in the February 28, 2000 submission will be posted in the N drive for review and discussion by all disciplines

/S/
Minutes Preparer

/S/
Concurrence, Chair
10/20/00

cc:
IND Arch:
HFD-580/DivFile

HFD-580/ Allen/Shames/Benson/Hoberman/ Rumble

drafted: Farinas, 8.28.00
concurrence: Shames 8.28.00/Gierhart 8.28.00/Chatterjee/Hoberman 8.28.00/Rumble 8.28.00
final: Farinas, 10.18.00

filename: .doc

MEETING MINUTES

Teleconference Minutes

Date: June 13, 2000 **Time:** 10:00-10:15 PM, EDT **Location:** Parklawn; 17B-43

NDA 21-228 **Drug:** Tolterodine [redacted] release **Indication:** [redacted]

Sponsor: Pharmacia & Upjohn

Type of Meeting: Guidance

Meeting Chair: Michael Ortwerth, Ph.D., Review Chemist, Division of New Drug Chemistry (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Mark Mannebach, Regulatory Affairs (for Gregory G. Shawaryn)

Meeting Recorder: Evelyn R. Farinas, R.Ph., Regulatory Project Manager

FDA Attendees:
Michael Ortwerth, Ph.D. – Review Chemist, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Mark Mannebach - Regulatory Affairs

Meeting Objective: To discuss and obtain concurrence from DRUDP regarding the Cincinnati District Office recommendations for batch validation.

Background: International Processing Corporation (IPC) sent a proposal for Process Validation to the Cincinnati District Office, dated May 3, 2000. The initial objective of the validation is to produce [redacted] of Tolterodine Tartrate [redacted] Release Beads. From the [redacted] lots produced, [redacted] of Tolterodine Tartrate [redacted] Release Capsules 2 mg and [redacted] of Tolterodine Tartrate [redacted] Release Capsules 4 mg will be produced. Division of lots in this manner is proposed to only be used during the process validation. Once production has been validated at IPC, each [redacted] only one strength of Tolterodine Tartrate [redacted] Release Capsule. IPC asked if the FDA agrees that it is acceptable for IPC to manufacture the process validation lots using this strategy of: 1) [redacted] and 2) [redacted] lots per strength of a substantial, but less than full-scale, size – i.e., about [redacted] and [redacted] (or the 4 mg strength). The FDA's Cincinnati District indicated that IPC's plan is acceptable. The sponsor is also seeking concurrence with the proposed plan from DRUDP.

Discussion:

- Comments and recommendations from the District Office regarding IPC's proposal were restated as follows:
  - The plan is acceptable (if all the details and the results are satisfactory) to justify distribution of these validation batches and any future split batches.
  - It is recommended that if and when the sponsor initiates [redacted] for each size), the sponsor continues with a concurrent validation of the first 3 batches of each.
  - The sponsor should repeat the validation testing on [redacted] batches of each strength.

Decisions made:

- District Office decision is acceptable provided that when the sponsor goes to full-scale production [redacted] concurrent validation of the first 3 batches of each will be continued
- The sponsor should repeat the validation testing on the [redacted] batches of each strength.

Action Items:

- Minutes will be sent to the sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-228
HFD-580/DivFile
HFD-580/Allen/Mann/Shames/Gierhart/Ortwerth/Rhee/Rumble/Farinas

drafted: erf/6.13.00
concurrence: Rhee 7.10.00/Ortwerth 6.14.00/Rumble 6.14.00
final: erf/7.10.00

MEETING MINUTES

Filing Meeting Minutes

Date: April 5, 2000 **Time:** 11:00-11:30 AM EST **Location:** PKLN; 17b-43

NDA 21-228 **Drug:** tolterodine [redacted] release capsules (no tradename)

Indication: [redacted]

Sponsor: Pharmacia & Upjohn Company

Type of Meeting: Filing meeting

Meeting Chair: Susan Allen, M.D., M.P.H., – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, RPh – Regulatory Project Manager

FDA Attendees:
Susan Allen, M.D., M.P.H. – Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D. – Medical Team Leader, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Michael Ortwerth, Ph.D. – Chemist, DNCD II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
D. J. Chatterjee, Ph.D.- Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Laurie McLeod, Ph.D.– Pharmacologist, DRUDP (HFD-580)
Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)
Shiew Mei Huang, Ph.D. – Acting Director for Division of Pharmaceutics Evaluation II (DPE II; HFD-870)
Evelyn R. Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss fileability of NDA 21-228 (tolterodine extended release).

Background: [redacted]

Discussion:
- concern regarding potential for dispensing errors if a tradename similar to Ditropan XL is chosen for this compound
- Clinical, Chemistry, Statistics, Clinical Pharmacology and Biopharmaceutics and Clinical Pharmacology and Toxicology reviewers indicated that there were no filing issues noted

Decisions reached:

- NDA 21-228 is fileable
- Sponsor will be asked to submit Biopharmaceutics data electronically (as previoulsy submitted in the CD as PDF format) in MS Word format
- Tradename consult will be send to OPDRA subsequent to sponsor's submission of proposed name for this product; Chemistry reviewer will request sponsor to submit trade name for review
- Label review will be done electronically
- DSI sites will be the same sites as those identified for NDA 20-771, S-004
- Financial disclosure section submitted is acceptable

Action Items:

- minutes will be provided to reviewers

/S/
Minutes Preparer

/S/ 5/1/00
Concurrence, Chair

cc:
NDA Arch: N21-228
HFD-580/DivFile
HFD-580/Allen/Mann/Shames/Gierhart/Parekh/Chatterjee/Jordan/McLeod/Rhee/Ortwerth/Rumble/Farinas
HFD-850/Huang

drafted: Farinas, 4.6.00
concurrence: Allen 5.1.00/Shames 4.11.00/Parekh/Chatterjee 4.11.00/McLeod/Rhee 4.14.00/Ortwerth 4.12.00/Rumble 4.7.00
final: Farinas, 5.1.00

MEETING MINUTES

D/F

Meeting Minutes

Date: November 3, 1999 **Time:** 1:00-2:30 **Location:** Parklawn, Chesapeake Room

Drug: tolterodine [redacted] release **Indication:** [redacted]

Sponsor: Pharmacia & Upjohn

Type of Meeting: pre-NDA guidance

Meeting Chair: Lisa Rarick, MD – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, RPh – Regulatory Project Manager

FDA Attendees:
Lisa Rarick, MD –Director, DRUDP (HFD-580)
Daniel Shames, MD – Medical Team Leader, DRUDP (HFD-580)
Mark Hirsch, MD – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Soraya Madani, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. – Statistical Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Moo-Johng Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Jackie White – CMC Team Leader
Henk De Koning Gans – Vice President Product Development, Urology
Ingrid Wallenbeck – Clinical Program Leader-Clinical Research Urology
Robert Schirmer- Medical
Johan Szamosi – Statistician Clinical research, Biostatistic and Data Management
Gregory Shawaryn – Regulatory Manager, US
Susan Mondabaugh – Regulatory
Christina Stahl – Regulatory Manager, Sweden
Ed Ciolkowski – Pharmaceutical Development, Drug Release

Meeting Objective: To answer sponsor's questions regarding plans for NDA submission of tolterodine [redacted] release capsule, and provide comments concerning data on *in vivo-in vitro* correlation for this product as well as the proposed capsule identification markings.

Background: Sponsor submitted questions on pre-clinical, clinical, statistical and package insert issues to obtain Division's feedback in preparation for NDA submission of tolterodine [redacted] release capsules (Serial No. 024, October 1, 1999). In addition, this meeting also addressed

sponsor's request for a Type A meeting seeking Division's input on information submitted regarding *in vivo-in vitro* correlation and stability data ("Proposed Drug Release Specifications for Tolterodine [redacted] Release Capsules Supported by a Level C *in vitro-in vivo* Correlation," Serial No. 025, October 13, 1999). Sponsor had submitted previously for the Division's review two reports in support of the use of metabolite (DD01) pharmacokinetic data as a basis for *in vitro/in vivo* correlation (Serial No. 14, April 21, 1999).

Discussion:

- Division answered the 9 questions submitted by sponsor:
  - cross-referencing to NDA 20-771 is acceptable; in addition, relevant sections should be incorporated into NDA submission for ease of review (i.e. Clinical data specific to the controlled release product)
  - cross-referencing nonclinical pharmacology/toxicology section to NDA 20-771 is acceptable; also, submitting an overall toxicology summary statement together with three preclinical studies of [redacted] products is acceptable
  - submission of one combined ISE and ISS report is acceptable
  - Division recommended that race be included as an additional subgroup analysis of efficacy; or a statement regarding race, if a subgroup analysis cannot be performed because the number of non-Caucasians in study is too small; analysis plan for determining if treatment effect varies by subgroup should be submitted
  - sponsor proposes [redacted] to tolterodine [redacted] release for 6 months at 4-month safety update, and [redacted] exposed for 1year at 8-months; Division requests original NDA submission contain data on 300 patients exposed for 6 months, with additional data at 4-month safety update; sponsor referred to previous agreement at August 12, 1998 meeting with Division indicating acceptance of safety data during NDA review; sponsor and Division may consider alternate proposals for submission of patient safety data
  - data provided in CD is acceptable; sponsor will provide statistical data analysis sets as SAS data sets and transport files
  - possible safety issue regarding immediate release formulation needs to be addressed before pediatric studies with the controlled release formulation begin
  - immediate release and controlled release package inserts should be harmonized as much as possible
  - based on a preliminary review of the submitted package insert, the following concerns were identified:
    - proposed dosing statement under **DOSAGE AND ADMINISTRATION** for patients with reduced hepatic function or who are currently taking drugs that are inhibitors of cytochrome P450 3A4 should be placed in a more prominent section of the label
    - to make labeling changes regarding clinical relevance of the study on the cat salivary gland, sponsor must submit overwhelming supporting data
    - results from invalidated quality of life instruments can not be incorporated into the label
    - regarding the Table of Contents, the Methods Validations Package that will be submitted as part of the NDA should include actual amount of samples that will be submitted to the FDA laboratory
- the following points were clarified concerning the *in vivo/in vitro* correlation (IVIVC):
  - one of the purposes of the IVIVC study is to establish meaningful *in vitro* dissolution specifications based on in-vivo performance of the dosage form

- the IVIVC data should be analyzed using parent compound *in vivo* concentrations and submitted for review in the NDA; this is because parent compound is considered to be more sensitive to changes in release rate of the drug than the metabolite
- ~~data using metabolite may also be submitted for consideration during the NDA review~~
- parent drug is the compound being absorbed, and is expected to be most sensitive in the release rates from the dosage form
- sponsor wants additional clarification regarding Division's preference for measurements in order to support broader specification range; Division needs to review CMC and Biopharmaceutics data before agreeing to a broader specification range

- sponsor indicated that dissolution method will remain unchanged and will not include the addition
- Chemistry comments:
  - comments regarding shelf-life specifications are premature; conclusions based on data will be made during the review of NDA
  - summaries submitted on IV/IVC correlation and shelf-life specifications have not been reviewed in detail; need to present all results so that Division can review in NDA
  - regarding stability data, it is acceptable for the sponsor to submit 3 data points (at 2, 4 and 6 months) at 40 degrees storage conditions
- Division does not favor due to potential safety concerns; the Office of Postmarketing Risk Assessment (OPDRA) will be consulted regarding precedents and CDER standards for inclusion/exclusion of identifying marking on tablets/capsules
- sponsor was asked to clarify data (parent to metabolite ratio) submitted in tables for food effect studies (Serial No. 25); specifically Division is seeking clarification if data presented was the mean of the ratios or the ratio of the means

Decisions reached:

- sponsor agreed to:
  - submit IVIVC data using parent compound
  - submit IVIVC data for the metabolite also
  - provide details of food effects studies in the NDA
  - provide the statistical methodology to be used for the subgroup analyses in the NDA
  - include race as a subgroup analysis or provide rationale why race is excluded
  - provide SAS data sets and transport files for the statistical review aid
- pediatric studies will not begin with the controlled release formulation until safety concerns with immediate release formulation have been resolved
- Division will consider and review alternate proposals regarding data (number of patients) to include at time of NDA submission, and at 4-month Safety Update
- dissolution method will remain unchanged and not include the addition of

Unresolved decisions: sponsor to propose number of patients with 6 months and 1 year exposure that will be included in original NDA and 4-month Safety Update.

Action Items:

- minutes will be provided to sponsor within 30 days
- OPDRA comments regarding logo imprint on capsule will be provided to sponsor (*CFR 206.10 allows as code imprint a mark, symbol, logo or monogram, combination of letters, numbers and marks or symbols)*

/S/ 12/3/99

Minutes Preparer

/S/

Concurrence, Chair

ADDENDUM:

November 4, 1999
Brief meeting held with FDA/Sponsor representatives
Parklawn, Potomac Room, 9:50-10:00 AM

FDA Attendees: Daniel Shames, MD
Mark Hirsch, MD
Evelyn Farinas, RPh

External Participants: Henk De Koning Gans, Vice President Product Development, Urology
Christina Stahl, Regulatory Manager, Sweden

Discussion:

- Sponsor and Division reviewed minutes from the August 12, 1998 meeting

Decisions reached:

- data from approximately 100 patients exposed to tolterodine [redacted] release for 6 months will be submitted at time of NDA submission
- data from 50 patients exposed to product for 1 year will be submitted at the 4-month Safety Update.

Action item:

- Sponsor will submit hard copy of agreement reached today regarding tolterodine [redacted] release.

cc:
IND Arch: [redacted]
HFD-580/DivFile

HFD-580/ Rarick/Shames/Hirsch/Rhee/Lin/Parekh/Madani/Kammerman/Rumble

drafted: Farinas, 11.04.99
concurrence: Rarick 11.09.99/Shames 11.05.99/Hirsch 11.05.99/Rhee 12.01.99/Lin 12.01.99/Parekh 12.02.99/Madani/Kammerman 11.09.99/Rumble 11.04.99
final: Farinas, 12.02.99

MEETING MINUTES

D/F

MEMORANDUM OF MEETING MINUTES

Date: March 10, 1999 **Time:** 12:00 pm – 1:00 pm **Location:** Pkln. 17B43

Sponsor: Pharmacia & Upjohn **Application:** [redacted] **Drug:** tolterodine

Type of Meeting: Pre-NDA; (CMC guidance)

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Randy Olmstead, Project Manager

FDA Attendees:
Mark Hirsch, M.D. - Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Dave Lin, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Soraya Madani, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Randy Olmstead, Project Manager, DRUDP (HFD-580)

External Attendees:
Jackie White, CMC Team Leader
Christopher Dick, QA Advisor, CMC documentation
Birgitta Olsson, Pharmacokineticist, Clinical Development Team Leader
Rut Tydell, Project Liaison Manager, Pharmaceutical Development
Annika Ohlsson, Senior Regulatory Manger, Sweden
Greg Shawaryn, Regulatory Manager, U.S.

Background: Sponsor requested a pre-NDA Chemistry meeting to discuss stability and the manufacturing process for tolterodine [redacted] release capsules.

Meeting Objective: To review and discuss the sponsor's meeting package and provide recommendations and comments on the information presented in support of a proposed NDA application.

Discussion Points:

Questions raised by the sponsor:

1. Only 9 months of stability data will be included in the original NDA for three batches of the 4 mg strength capsule. Accelerated data will be available through six months. Plans to submit within 4-6 months of filing, additional data which will include 12 months of real time data. Does the FDA agree with the proposed amendment and that this would not extend the review clock?

   Answer: The proposed time frames are acceptable.

2. In addition to that already approved in the NDA for Detrol tablets, an [redacted] method, manufacturing site and source will be included for the active pharmaceutical ingredient, tolterodine tartrate. In the original NDA, we proposed to include at least 3 months of stability data for one batch of 4 mg strength capsules made with this new material. Data will be presented for all market packages. Does the FDA agree that the stability strategy is acceptable for approval to use the new process material?

   Answer: Historical data should be submitted for the [redacted] for comparison to the new method. Chromatographs on any impurities should be provided. Full characterization and comparison of particle size prior to [redacted] should be submitted.

3. A 2 mg strength capsule will also be included in the original NDA. The manufacturing process will be the same as for the 4 mg strength except for capsule fill. A smaller capsule size will be used. In the original NDA, we propose to include at least 3 months of stability data for three batches of the 2 mg strength capsules manufactured with new process drug. Does the FDA agree that the stability strategy is acceptable for approval of the lower strength capsule?

   Answer: If the [redacted] are the same for the 4 and 2 mg capsule, then 6 months of accelerated data would be requested at the time of submission due to the capsules not being the same. If at time of filing, there is only 3 months of accelerated data, then the additional data up to 6 months could be submitted as an amendment. The number of lots is acceptable.

4. A strategy for establishing drug release specifications is proposed. Does the FDA have any comments/questions?

   Answer: To determine which method correlates the best, the sponsor should use the guidance document as a reference.

5. A rationale is presented for using metabolite DD01 pharmacokinetic data rather than tolterodine data for describing drug release and absorption from oral extended release preparations of tolterodine. Does the FDA agree that this approach is appropriate and that it is acceptable to base *in vitro/in vivo* correlations on DD01 data?

   Answer: The sponsor should submit as much data as possible to justify the use of DD01 for establishing IVIVC. Comments will be provided following review of these data.

6. The color of the capsule may need to be changed. Removal of pigment of the current [redacted] is one option. Another option is a change to a completely different color. What data would need to be supplied at the time of filing if either of the above changes were made?

   Answer: For either a complete color change or modification of the existing color, 6 months of accelerated data would be expected. If 6 months of data can not be submitted at time of filing, 3 months would be needed at filing and a minimum of 3 additional months as an amendment. For a new color, the expiration date may be affected by the limited stability data.

Action Items:

1. Exchange meeting minutes with sponsor within 30 days.
2. Sponsor will submit data to the *in vitro / in vivo* working group for review.

/S/

Meeting Recorder

/S/

Meeting Chair

cc.

HFD-580/ [redacted]
HFD-580/Div File
HFD-580/Mann/Hirsch/Rhee/Lin/Parekh/Madani/
Concur/rumble 4.6.99/Lin 4.6.99/Parekh 4.6.99/Madani 4.6.99/Hirsch 4.7.99/ Rhee 4.8.99
Final/ olmstead 4.8.99

NDA 21-228
Detrol (tolterodine tartrate) extended release
Pharmacia and Upjohn Company

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 21-228
Detrol (tolterodine tartrate) extended release
Pharmacia and Upjohn Company

Federal Register Notices

This application was not the subject of any Federal Register Notices.

APPEARS THIS WAY
ON ORIGINAL

K1.2

K1.2

Rec'd 12-28-00 MC

N21228

N21228

NDA 21-228

Tolterodine Extended Release Capsules

Action Package - Volume Two

Deputy Director/Team Leader Memorandum

NDA: 21-228
Date submitted: 2/25/00
Review completed: 12/22/00

Sponsor: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

Drug names:
Generic: Tolterodine tartrate extended release capsules
Trade:
Chemical: (R)-N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropropanamine L-hydrogen tartrate

Drug class: Muscarinic receptor antagonist

Administration route: Oral

Dosage form: Extended release capsule qAM

Strength: 2 mg and 4 mg

Proposed indication:

REGULATORY BACKGROUND

Tolterodine immediate release tablets (Detrol™ Tablets) were approved by the agency on March 25, 1998 for the treatment of patients with an **overactive bladder** with symptoms of urinary frequency, urgency, **or** urge incontinence. The sponsor now submits their first tolterodine modified release dosage form in **NDA 21-228** for **tolterodine release capsules.** It should be noted that the modifier " " is not an official dosage form in the United States Pharmacopoeia (USP) monographs. The term "extended release" is used for Pharmacopoeia purposes. Tolterodine extended release (ER) capsules were evaluated in seven clinical trials enrolling 1659 patients. The Clinical/Statistical Data of **NDA 21-228** contains the final study reports of five phase 1 clinical pharmacology trials: **97-TOCR-001, 97-TOCR-003, 98-TOCR-005, 98-TOCR-006, and 98-TOCR-010**; one phase 2 clinical pharmacology and dose-finding trial **97-TOCR-002**; and **one phase 3 clinical trial, 98-TOCR-007,** with a long-term extension, **98-TOCR-007B.**

NDA CLINICAL INFORMATION

Conduct of the Clinical Trial: Study **98-TOCR-007** was a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, parallel design study in adult patients with urinary frequency and urge incontinence. The study had three equally sized arms: tolterodine ER capsules 4 mg qAM, tolterodine IR tablets 2 mg bid, and placebo. The study was comprised of three periods: a 1- to 2-week wash-out/run-in period, a 12-week treatment period, and a 1-week follow-up period. The primary efficacy endpoint was the change in number of incontinence episodes per week from baseline to week 12. A total of 1529 patients were randomized to treatment at 167 sites in 14 countries.

Efficacy Results: The primary efficacy variable for Study **98-TOCR-007** was the number of **incontinence episodes per week**, as calculated from data recorded urinary diaries. A decrease in the mean number of incontinence episodes per week at end of study (week 12) from baseline was demonstrated by tolterodine ER (-11.8 episodes or 53%) and placebo (-6.9 episodes or 30%). The treatment difference between tolterodine ER and placebo was 4.8 incontinence episodes per week, which was **statistically significant** (p=.0001). Limited efficacy data is available for tolterodine ER 2 mg, since it was evaluated in only 29 patients in the Phase 2 dose-effect study 97-TOCR-002.

Reviewer's comment: It is appropriate to approve the 2 mg dose because medications in this class of drugs are often titrated lower in patients if tolerability issues occur (i.e. dry mouth, constipation, etc.) and efficacy can be expected at the lower dose. Detrol — initial recommended dose is 2 mg bid but "The dose may be lowered to 1 mg bid based on individual response and tolerability". Although, the 2 mg ER dose was only evaluated directly in 29 patients, the biopharmaceutics reviewer concluded that that Detrol — and ER are equivalent in terms of AUC at the same daily doses (e.g. Detrol — 1 mg is "equivalent"to Detrol 2 mg ER qd.)

Safety Results:

General: Dry mouth, constipation, and headache were the most frequent adverse events reported with tolterodine ER. No new major safety concerns were evident from the review of tolterodine ER reported adverse events, serious adverse events, premature withdrawals, ECG and clinical laboratory assessments when compared to the safety concerns previously reported with tolterodine —

Differences in the safety profile of tolterodine ER 4 mg qAM were identified based on age, gender, and metabolism. Increased incidence of dry mouth, constipation and headache were reported in women, in the elderly (>65 years), and in extensive metabolizes, but these results were not thought to be clinically significant.

QT Interval Changes: Tolterodine is structurally related to terodiline, which was withdrawn from markets outside the US because of cardiac abnormalities related to QT

interval prolongation. Therefore, the sponsor was asked to evaluate QT interval changes during controlled trials.

In this NDA, EKGs were obtained in a total of 174 patients (placebo=54, tolterodine ER=59, tolterodine [illegible]=61) in selected centers in the United States. Mean QTc increased 2.7 msec in the tolterodine ER group and decreased 3.5 msec in the placebo group. The sponsor and the primary medical reviewer concluded that there was no evidence of disturbing QT interval changes in this NDA.

Reviewer's comment: A consultation was obtained by DRUDP from DCRDP regarding the QT issue. The consultant did not find any data in the NDA that was disturbing but recommended in vitro and in vivo studies of the potential for QT prolongation and tolterodine use. She further recommended that "our suspicions (that tolterodine might prolong QT interval) should be stated in the product label so physicians can decide if it is worth the risk" because "tolterodine is the R-enantiomer of terodiline"(evaluation by the DRUDP chemistry team concluded that is an incorrect statement) and a dog study indicated a 10 to 20% prolongation of QT interval 68 times the recommended dose.

Dr. Marianne Mann performed an extensive review of tolterodine and QT prolongation in January 2000 when she was Deputy Director of DRUDP. Her conclusions were based on an OPDRA consult of post-marketing reports after approximately 4 million prescriptions for tolterodine were issued and post marketing reports of other anticholingeric medications, a cardiorenal consult and her own review of the IR tolterodine NDA data.

The current product labeling for IR tolterodine contains a reference to the possibility of QT interval prolongation with tolterodine overdose (this is found in the OVERDOSAGE Section). Dr. Mann concluded, with the concurrence of the ODE-III Office Director and Deputy as well as the Division Director that "This labeling is felt to accurately reflect the risks of tolterodine regarding QT interval changes, and no other changes are recommended at this time" **(see Dr. Mann's review which is attached).**

<u>I agree with the primary medical officer that there is insufficient data to place an additional cautionary statement regarding tolterodine ER and QT prolongation in the label at this time.</u> The sponsor proposed to

INTERGRATED COMMENT REGARDING EFICACY AND SAFETY
I believe that Detrol LA is safe and effective for the indication of overactive bladder. I agree with the primary medical officer's recommendation of <u>approval.</u>

NDA PRECLINICAL INFORMATION

Because tolterodine was approved as an IR product and the ER product gives comparable daily exposures while reducing the maximum concentration, no new animal studies were required for the parent compound. However, in accordance with ICH guidelines, two in-vitro genotoxicity studies and a three month general toxicity study in mice were performed on two tolterodine degradation products that might [redacted] by the end of the proposed shelf life. These studies did not reveal any additional toxicity of these compounds at 2% of the parent compound dose. The toxicology review team recommended approval of this NDA.

Reviewer's comment: I agree with the toxicology review teams recommendation of approval.

NDA CHEMISTRY INFORMATION

All matters related to CMC of the product were found to be approvable by the chemistry team with the exception of the tradename issue which is explained below. The EER 's were found to be acceptable by the Office of Compliance.

The original tradename proposed by the sponsor was [redacted]. This was rejected by OPDRA and the Division because of the potential for medication errors related to other products with the [redacted] The Division and OPDRA proposed **LA** as an acceptable suffix. On 12/7/00, the sponsor submitted a tradename proposal of [redacted] Although this submission was too late in the review cycle for a formal OPDRA evaluation, there were internal discussions between OPDRA and the Division about this proposed suffix. The consensus was that the [redacted] was also unacceptable because of concerns regarding medication errors.

This opinion was relayed to the sponsor by the Division's Chief of Project Management Staff on 12/13/00 during a tcon. The various regulatory options were offered to the sponsor including withdrawing the unacceptable tradename, or withdrawing all tradenames and receiving a possible approval action or continuing to negotiate the tradename issue and receiving a possible approvable action.

Reviewer's comment: I agree with chemistry team's recommendation of approval.

NDA BIOPHARMACEUTICS INFORMATION

The biopharmaceutics review team believes that NDA 21-228 is **acceptable.** There are multiple suggested labeling modifications related to drug/drug interactions and special populations. The sponsor has proposed a IVIVC analysis which is currently under review by the Biopharm. Team. The IV/IVC review will not be complete by the action date but this is not an approvability issue.

Reviewer's comment: I agree with the biopharmacology team's recommendation of "acceptable".

DSI

Three clinical site were inspected and minor violations were found at one site(Dr. Freedman). The final recommendation of DSI was that the data submitted in support of the NDA from all the inspected sites are acceptable.
Reviewer's comment: I agree with DSI's assessment of acceptable.

PEDIATRIC INFORMATION
The study of pediatric patients in the context of the Pediatric Rule and pediatric exclusivity was discussed with sponsor during a 11/29/00 teleconference. The following issues will be addressed by the appropriate regulatory mechanisms:

- [redacted] is to be developed and studied [redacted]
- [redacted]
- [redacted]
- Submission of the reports for the above studies will be deferred until 12/15/02.

Reviewer's comment: I agree with the pediatric plan

LABELING ISSUES
The following are the main issues were negotiated with the sponsor regarding labeling:

- **Tradename**: Sponsor proposed [redacted]. The Division and OPDRA proposed Detrol LA because of the potential for medication errors with the sponsor's proposals. As of 12/18/00, the sponsor has agreed to Detrol LA.
- **Pharmacology**: The Division and the sponsor [redacted]
- **Indication:** The sponsor proposed [redacted] The Division proposes "and" because it is most appropriate to the trial population and it is consistent with other drugs in this class.
- **Efficacy endpoint:** For labeling consistency, trial results will be expressed as incontinence episodes per week, rather than day.
- **OPDRA Consult**: The OPDRA consultant recommends information in the PPI regarding the difference between Detrol and Detrol LA. However, neither Detrol nor Detrol LA has an associated PPI. Other comments made by OPDRA reviewer's concerning primary and secondary drug product

packaging and the drug product dosage form were found not applicable by the chemistry review team.

Recommended Regulatory Action

I agree with opinions of all regulatory review teams and recommend approval of Detrol LA.

/S/

I concur.

Daniel A. Shames MD FACS
Deputy Director, DRUDP

/S/
12/22/00

APPEARS THIS WAY
ON ORIGINAL

D/F

Memorandum
From: Marianne Mann, M.D., Deputy Director
To: NDA 20-771
Regarding: QT prolongation with Detrol™ (toleterodine tartrate tablets)
Date Completed: January 24, 2000

Background
Tolterodine is marketed by Pharmacia and Upjohn and was approved by the FDA on March 25, 1998 for the treatment of patients with overactive bladder who have symptoms of urinary frequency, urgency, or urge incontinence. IMS Health National Prescription Audit data include a total prescription use as follows:

On June 16, 1999 the sponsor submitted a 15-day adverse event report of a case of Torsade de Pointes (TDP). Following this submission, our Division responded with several internal meetings, a teleconference with the sponsor, and multiple consults to the Division of Cardiorenal Drug Products (DCRP) and the Office of Post-Marketing Drug Risk Assessment (OPDRA). The purpose of this memorandum is to briefly summarize the issues and concerns regarding the occurrence of this case, and to provide a final Division recommendation.

The Index Case
A thorough review of the index case resulted in many possible etiologies for arrhythmia other than drug-induced TDP. The patient was a 57 year old male with a past history of atrial fibrillation (on no treatment), arthritis and a goiter. He had a prior history of heavy alcohol/smoking use. In September of 1998 he began tolterodine 2 mg twice daily due to bladder symptoms. Approximately 6 months later, on March 15, 1999, he was admitted to the hospital for bladder surgery. At that time the patient was taking diclofenac, allopurinol, tolterodine and codeine/paracetamol. His ECG on admission revealed atrial fibrillation with a ventricular rate of 165 bpm, so a cardiac evaluation was pursued. Due to persistent atrial arrhtymias, surgery was cancelled and an exercise test was pursued.

On March 18th, the patient underwent the exercise test. During the test, he developed deep ST segment depressions and atrial fibrillation with a fast ventricular response, which deteriorated into a rapid, irregular, broad QRS complex tachycardia. The tachycardia developed during peak exercise and was felt to be most likely due to coronary ischemia. QT intervals were examined before, during, and after the tachycardia event, and increases in this interval were not noted.

Reviewer's comment:
It is reasonable to conclude that the most likely cause of this patients TDP was ischemia, and that a drug-induced etiology was less likely due to the lack of QT interval changes in the ECG surrounding the event. Thus, the index case itself is not very impressive. Tolterodine, however, is chemically related in structure to a previous drug (Terolidine), which was approved in Europe, and which produced TDP and prolonged QT intervals after marketing. These events results in Terolidine's withdrawal from the market. Additional review of Tolterodine was therefore pursued, including a Cardio-Renal consult of the original NDA data, and additional OPDRA consults of the post-marketing data.

The Cardio-Renal Consult
Dr. John Koerner from HFD-110 reviewed the animal toxicology data with Dr. Alex Jordan (HFD-580). The results of this review, briefly, revealed that tolterodine prolonged the QT interval in dogs in a dose dependent manner, although the doses at which this occurred were many times (30 fold and 100 fold) the exposures in humans at the approved dose of 2 mg bid. Dr. Koerner recommended that the effects of tolterodine on the Ikr (rapidly activating delayed rectifier) be examined in vitro by the sponsor. In addition, he noted that the results of this study would, most likely, be positive—given the positive effects noted in animal studies with tolterodine.

Dr. Maryann Gordon from HFD-110 reviewed the clinical case data and data submitted by the sponsor on QT interval changes as assessed in smaller phase 2 studies. She recommended that the sponsor pursue a clinical study of the effects of increasing doses of tolterodine (to be given to a maximally tolerated dose) on the QT and QTc intervals studying poor metabolizers of tolterodine. (Approximately 10% of the adult population are felt to be poor metabolizers of tolterodine due to their 2D-6 metabolizing status.)

Of note, both Drs. Gordon and Koerner agreed that the index case itself was not particularly convincing. The structural similarity of tolterodine to terolidine was concerning to them, however. Dr. Koerner noted that the current "state-of-the-art" Ikr study was not available at the time this drug was developed, so it was not surprising that this study was not performed by the sponsor. Dr. Gordon noted that her major concern focused on poor metabolizers of tolterodine, who may be exposed to higher serum concentrations—and who therefore may be at greater risk for potential effects on the QT interval.

Review of Clinical QT Studies in NDA
Several studies involving a variety of doses of tolterodine in small numbers of patients were included in the original NDA submission. These studies and the mean results on QT and QT_c are summarized in the following table.

Extensive Metabolizers	Dose	QT (ms) Baseline/change	QT_c (ms) Baseline/change
Study 92-OATA-001 in 11 subjects	2 bid	418/-8	414/-2
Study 92-OATA-001 in 11 subjects	4 bid	414/-16	414/+7
Study 93-OATA-004 in 6 elderly subjects	4 bid	412/-7	407/+2
Study 94-OATA-013 in 12 subjects	1 bid	392/+5	403/0
Study 94-OATA-013 in 10 subjects	2 bid	392/-5	403/-1
Study 93-OATA-007 in 11 subjects	2 bid	413/-19	433/-14
Poor Metabolizers			
Study 93-OATA-004 in 6 elderly subjects	**4 bid**	**392/+29**	**403/+14**
Study 94-OATA-013 in 2 subjects	1 bid	392/+6	403/+14
Study 94-OATA-013 in 2 subjects	2 bid	392/+11	403/+11
Study 93-OATA-007 in 1 subject	1 bid	413/+17	433/-11

Reviewer's Comment:
The mean changes in QT and QT_c are largely unremarkable with the exception of Study 93-OATA-004, which was performed in 6 elderly subjects, all of whom were poor 2D-6 metabolizers. This study leads to concern that the mean increase in QT interval of +29 ms and in QT_c interval of +14 ms could be a drug-related effect. Due to this concern, scatter plots of QT and QT_c interval changes for individual subjects for all of the above studies were requested.

The sponsor provided the scatter plots of all studies where QT interval changes were assessed. Some additional studies (not outlined in the above table) were reported with these scatter plots. These included studies 92-OATA-002, 92-OATA-003, 92-OATA-005, 93-OATA-006, 94-OATA-009, and 94-OATA-012). All studies involved doses of tolterodine of up to 4 mg BID (twice the approved dose). (Scatterplots from all studies are attached to this review.)

Overall, the changes in QT and QT_c were not impressive for these scatterplots, and many of the changes in QT were centered around 0, and only a rare patient exceeded a change from baseline of 50 ms increase/decrease in either QT or QTc interval. The study of concern was study 93-OATA-004. This study

revealed that while the extensive metabolizers change in QT and QT_c were centered around 0 and did not increase/decrease by more than approximately 20 ms, the poor metabolizers had a somewhat different result. Most of the poor metabolizers experienced an modest increase in their QT and QT_c, with 3 patients experiencing a more marked increase in QT_c above 40 ms (i.e one patient increased their QTc by approximately 40 ms, one patient by approximately 70 ms, and one patient by approximately 80 ms). This was not a placebo-controlled study, however, so additional placebo patient data was reviewed in the clinical trials presented. Study 93-OATA-007 notably included 2 placebo-treated subjects who likewise experienced an increase in their QTc above 60 milleseconds. Thus, although two poor metabolizers in study 93-OATA-004 had concerning QTc increases, this same phenomenon was noted in placebo-treated patients in a separate study.

Reviewer's comment:
The scatterplots of individual patient data support concern that poor metabolizers who received a 4 mg BID dose of tolterodine (twice the recommended dose) tended to experience a modest increase in their QTc intervals. Three patients experienced a QTc interval change exceeding 40 ms, of whom two exceeded 60 ms. However, in a separate study including placebo-controlled data, similar changes in the QTc interval were observed.

At a recent FDA Advisory Panel Meeting (for Moxifloxacin, held 10/21/99), the Eastern European's Committee for Proprietary Medical Products (CPMP) noted that they had published a "Points for Consideration" document concerning QTc interval changes and their clinical implications. Dr. Morganroth, who spoke for Bayer Pharmaceuticals at this meeting explained these points as follows. "The CPMP advises that there is no concern in the QTc interval change is less than 30 ms. A change between 30 and 60 ms suggests the possibility that the drug could cause clinical cardiac effects. Concern about cardiac events should be raised if the QTc interval changes by greater than 60 ms."

Based on these comments, there is concern that tolterodine could have clinically relevant effects on QTc intervals in poor metabolizers who might receive more than the recommended 2 mg BID dose of tolterodine. This concern is off-set, however, by the finding of similar increments in the QTc interval even among placebo subjects.

Postmarketing Perspective from OPDRA
OPDRA performed several consults with regard to this case. The December 23, 1999 report on events of QT prolongation and ventricular arrhythmias with a variety of anticholinergic drugs used to treat incontinence provides some useful perspective.

This report reviewed the following anticholinergic drugs used to treat incontinence:

- Urised
- Urispaz
- Cytospac
- Ditropan
- Detrol

First, labeling was reviewed for each product:

- Urised: contains no information about adverse cardiac events
- Urispaz: contains palpitations and tachycardia as cardiac events
- Cytospac: contains palpitations and tachycardia as cardiac events
- Ditropan: contains palpitations, tachycardia and vasodilation as cardiac events
- Detrol: contains hypotension as an adverse cardiac event. Under management of overdose, the labeling provides the following information: ECG monitoring is recommended in the event of overdose. In dogs, changes in the QT interval (slight prolongation of 10 to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed at doses up to 4 mg twice daily of tolterodine (higher doses were not evaluated.)

Second, drug prescription use from 1996-1999 based on IMS data was reviewed for each product:

- Urised:
- Urispaz:
- Cytospac (including Cytospaz-M, Levbid, Levsin, Levsin w/PB, Levsin/SL, Levsinex, and Levsinex w/PB):
- Ditropan (including Ditropan XL):
- Detrol:

Third, a drug search for each drug was performed using the following terms: *ventricular arrythmia, cardiac arrest* as MEDDRA HLT term and *electrocardiogram QT prolonged, syncope, and sudden death unexplained* as MEDDRA PT terms. The search produced the following:

- Urised: no cases
- Urispaz: 1 case of syncope attributed to patients uncontrolled diabetes
- Cytospac: 5 cases. Four cases of cardiac arrest/death, anaphylaxis/death, tachycardia/death, and ventricular fibrillation/tachycardia. One case of syncope in a patient with a history of migraines. The most compelling case was a 78 year old male who developed transient ventricular fibrillation and a rapid pulse for 2 weeks after taking Levsinex in conjunction with Norvasc.

The patient had been taking Norvasc for approximately 2 years, while the duration of Levsinex use was unknown. Concomitant medication included Inderal. Past history included prostate surgery and paroxysmal atrial tachycardia for many years.

- Ditropan: 11 cases. Four cases of ventricular extrasystole/tachycardia, bigeminy/coma, cardiac arrest/death, and QT prolongation. Five cases of syncope. Two cases were of particular concern. A QT prolongation case involved a patient of unknown age/gender who experienced QT prolongation after receiving an overdose (amount unknown) of Ditropan. The patient died one year after the event; it is unknown if the death was related to the event. Concomitant medications and past history were unknown. The second case of concern was an 84 year old male who developed torsade de pointes when oxybutynin (dose/duration unspecified) was added to his medical regimen of digoxin and atenolol. He recovered when all medications were stopped.
- Detrol: 17 cases. Twelve cases of syncope appeared to be related to causes other than tolterodine. Of the remaining 5 cases, one was the index case descried previously in this report. Of the remaining 4 cases, two were cardiac arrests. A 69 year old man experienced a myocardial infarction one day after taking 4 mg tolterodine. He had a history of angina. An 83 year old man experienced a fatal cardiac arrest after receiving tolterodine (dose/duration unknown) tot reat urgency. Finally, there were 2 cases of syncope. A 71 year old male developed syncope and "ended up at the bottom of the pool" after taking 4 mg of tolterodine for 28 days to treat incontinence. Tolterodine was discontinued, and he recovered with no residual effects. He had a history of atrial fibrillation/flutter and was also on digoxin. The final case was a patient (unknown gender/age) who experienced dizziness and blacked out while taking 2 mg tolterodine/day for unknown duration.

Reviewer's Comment:
The post-marketing cases presented with tolterodine do not appear particularly concerning in the context of similar cases being reported with Ditropan and Cytospac. Thus, the post-marketing signal for concern with tolterodine appears no greater than that of other approved anticholinergic drugs for the same indication.

In addition, the original OPDRA consult received regarding the index case of TDP with tolterodine makes the following conclusions:

"The index case of cardiac arrhythmia associated with tolterodine use is disturbing; however the patient's cardiologist ruled out TDP. Given the patient's cardiac history, it is difficult to link the use of tolterodine with the cardiac arrhythmia reported. To date, no additional cases indicating life-threatening ventricular arrhythmia have been identified in AERS or the literature....The labeling discusses QT interval prolongation observed in animal studies using high doses of tolterodine only in the *management of overdose* section.

Consideration should be given to placing this information in the *pharmacology* section of tolterodine labeling as well. We will continue to monitor tolterodine closely for additional cardiac arrhythmias and update you if more information becomes available, particularly in light of the arrhythmia potential of the related drug, terolidine."

Reviewer's Conclusions

There are several conclusions to be drawn from this review which do not support a regulatory action to require additional studies of the sponsor.

1. The index case of "TDP" is not a strong case with regards to relating this event to tolterodine.
2. The reporting of postmarketing cardiac events with other anticholinergic drugs for incontinence is similar to that noted with tolterodine. Thus, if tolterodine were felt to cause QT prolongation based on the index case, then all anticholinergic drugs for incontinence would have to be viewed similarly.
3. The labeling for tolterodine with regard to QT prolongation is stronger than that for any of the approved anticholinergic agents for incontinence (albeit with information given only in the drug overdose section).
4. The effects of tolterodine on QT and QTc intervals were studied in multiple phase 2 clinical trials. Results demonstrate that the effects of tolterodine are generally similar to those of placebo. The study of potential concern involved poor metabolizers who experienced an increase in their QTc interval upon receiving 4 mg bid of tolterodine, with 2 subjects experiencing increases $\geq$ 60 msec. This data was not placebo-controlled, but other study data from study 93-OATA-007 documented similar findings among placebo-treated subjects.

Conversely, there are some conclusions that lead to concern:

1. Tolterodine is related chemically to terolodine, an agent that was pulled from the European market after cases of TDP were reported.
2. Tolterodine has effects on the QT interval in animals, albeit at concentrations much higher than those noted in humans at the approved dose.
3. The study results in poor versus extensive metabolizers, while not placebo-controlled, could be considered suggestive of a modest effect on QTc by doses of tolterodine at twice the recommended dose.

It is worth noting that the other approved anticholinergic agents for incontinence (being much more dated in their approvals) have not performed similar extensive preclinical and clinical evaluations to assess their potential effect on the QT. Requiring Pharmacia and Upjohn to further pursue their studies (because known results in poor metabolizers are somewhat concerning) would, in this reviewer's opinion, lead to a requirement of studies by other sponsors. Given the wide use of these products and the very low reporting rate of postmarketing adverse cardiac events overall, this approach is not supported.

Therefore, although I agree with the cardiology consultants that patients who are poor metabolizers of tolterodine may be at risk for prolonged QT (particularly if a dose above the recommended 2 mg is taken), I do not feel this supports requiring additional studies of the sponsor. Should additional reports suggestive of QT prolongation be reported to the agency, however, I agree that a study of a maximally tolerated dose in poor metabolizers could provide useful information about the safety range of tolterodine in this patient population. The decision to require this of Pharmacia Upjohn would, of course, depend upon the number and quality of reports submitted.

The current product labeling for tolterodine states in the Overdosage Section:

Management of Overdosage
Overdosage with Detrol can potentially result in severe central anticholingeric effects and should be treated accordingly.

ECG monitoring is recommended in the event of overdosage. In Dogs, changes in the QT interval (slight prolongation of 10 to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was not observed at doses up to 4 mg tice daily of tolterodine (higher doses were not evaluated).

This labeling is felt to accurately reflect the risks of tolterodine regarding QT interval changes, and no other changes are recommended at this time.

These data were discussed at multiple meetings, including a 1/14/00 meeting between Dr. Florence Hbun and Dr. Victor Raczowski of ODE-III, and Dr. Susan Allen and myself, with concurrence from each present as to these conclusions.

/S/
Marianne Mann, M.D.
Deputy Director, HFD-580

/S/ 1/28/00
Susan Allen, M.D. (for concurrence)
Acting Director, HFD-580

/S/ 2/2/00
Florence Houn, M.D. (for concurrence)
Director, ODE-III

/S/ 2-1-00
Victor Raczowski, M.D. (for concurrence)
Deputy Director, ODE-III

(1) I CONCUR THAT CHANGES TO THE LABELING ARE NOT NECESSARY AT THIS TIME.

(2) THE STRUCTURAL SIMILARITY TO TEROLIDINE AND DOSE-RELATED INCREASES IN QT DURATION IN ANIMALS ARE WORRISOME, BUT CLINICAL DATA ARE LIMITED BECAUSE OF SMALL NUMBERS OF SUBJECTS IN STUDIES, LACK OF CONTROL GROUPS, ~~etc.~~ MAGNITUDE OF QT CHANGES LARGELY UNIMPRESSIVE, ETC.

(3) ~~Pg.~~ IF TOLTERODINE PROLONGS QTc IN HUMANS, IT MAY DO SO IN WAYS UNRELATED TO ITS ANTICHOLINERGIC PROPERTIES. I DISAGREE WITH THE IMPLICATION THAT THIS ~~would~~ MUST be a class EFFECT OF ANTICHOLINERGIC DRUGS

/S/ 2-1-00

cc—
NDA 20-771
Houn/ODE-III Director
Raczowski/ODE-III Deputy Director
Allens/HFD-580 Acting Director
Jordan/HFD-580 Pharm Tox Team Leader
Gordan/DCRDP
Koerner/DCRDP
Rodriguez/OPDRA Director
Corkin/OPDRA Safety Evaluator
Farinas/HFD-580 Project Manager