CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-771/S-004

ADMINISTRATIVE DOCUMENTS

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Patent statement
Action:	Refer to patent information correspondence from sponsor dated May 1, 2000
Date:	April 3, 2001

Form Ver. 1

PATENT SUBMISSION FORM

Patent Information Pursuant to 21 C.F.R. 314.53

For

NDA # 020771

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: DETROL
- Active Ingredient(s): Tolterodine Tartrate
- Strength(s): 1 mg, 2 mg
- Dosage Form: Tablet
- Approval Date: March 25, 1998

A. This section should be completed for each individual patent.

For more than three patents, copy and paste this section as many times as needed.

U.S. Patent Number: 5,559,269

Expiration Date: May 5, 2015

Type of Patent – Indicate all that apply:

1) Drug Substance (Active Ingredient) _X_ Y ___ N
2) Drug Product (Composition/Formulation) ___ Y _X_ N
3) Method of Use _X_ Y ___ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

Name of Patent Owner: Pharmacia AB

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,559,269 covers the composition, formulation and/or method of use of DETROL (name of drug product). This product is:

* X currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act

OR

* __ the subject of this application for which approval is being sought

---

Signed: Don W. Schmitz
Date: 4/25/00
Title: Corporate Secretary

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within thirty (30) days of the date of issuance of the patent.

To expedite publication in "***The Orange Book***," a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR

Fax to: (301) 594-6463

* Please note that patents for unapproved compositions, formulations or uses will NOT be published in ***The Orange Book***.

EXCLUSIVITY SUMMARY for NDA # 20-771 SUPPL # 004
Trade Name Detrol Generic Name tolterodine tartrate tablets
Applicant Name Pharmacia & Upjohn Corporation HFD- 580
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /x__/

   b) Is it an effectiveness supplement? YES /x__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE 8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /___/ NO /x__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_x__/ NO /___/

If yes, NDA # 20-771__ Drug Name Detrol

Note: No product other than Detrol (with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule) has been previously approved by FDA for the same use. The clinical studies were submitted to support the change in wording from " Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence" to "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency and urge incontinence"

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the

upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

(S) April 2/01

Signature of Preparer Date

Title: Project Manager

(S) 4/2/01

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Pediatric Rule
Action:	Not applicable for this application
Date:	April 3, 2001

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Debarment certification
Action:	Refer to debarment certification dated December 15, 1999
Date:	April 3, 2001

DEBARMENT CERTIFICATION FOR TOLTERODINE Efficacy Supplement
NDA # 20-771

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ed L. Patt — 12/15/99

Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 17, 2000 LLP 10/17/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 20-771)

I have reviewed the financial disclosure information submitted by Pharmacia & Upjohn in support of their supplemental NDA, NDA 20-771/S-004.

One large clinical trial was conducted to support the safety and efficacy for Detrol (tolterodinee) for use as monotherapy in the treatment of advanced prostate cancer. The study number and its respective outcome with regard to financial disclosure obligations is summarized below.

Study No.	Study Status	Financial Disclosure Documentation
98-TOCR-007	Ongoing as of February 2, 1999	Appropriate documentation; two investigators reported financial interest (see notes below)

Of those investigators not reporting financial interest, there was a 96% compliance rate in completing the appropriate paper work.

[redacted] reported receiving greater thar [redacted] rom P & U for "assistance with development of a urodynamic unit. [redacted]. Sufficient monitoring of the site was performed, and this receipt of money has no impact on the outcome of the study.

[redacted] reported receivin [redacted] rom P & U for "an educational grant for a research nurse.' [redacted] Sufficient monitoring of the site was performed, and the site was part of the clinical audit that was conducted by the Agency. This receipt of money has no impact on the outcome of the study.

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

OCT 6 2000

Deputy Division Director's Memorandum
Multiple Labeling Revisions

NDA: 20-771
Tolterodine Immediate Release (Detrol™)

Primary

Secondary
SE8-004 (Supplement-Labeling Revision with Clinical Information)
Submitted: 12/22/99

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

Drug names:
Generic: Tolterodine tartrate immediate release tablets
Trade: Detrol™
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: Immediate Release tablets BID

Strength: 1 mg and 2 mg

Indication: Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

BACKGROUND

The Detrol™ original NDA 20-771 was submitted on March 24, 1997 and was approved on March 25, 1998. The fourth supplemental submission for NDA 20-771 is submission **SE8-004** (Supplement-Labeling Revision with Clinical Information) which was submitted on December 22, 1999. It presents clinical data from Protocol **98-TOCR-007**, which was performed under IND 56,406. The clinical section of this efficacy supplement consists of one study report, **98-TOCR-007**. Study **98-TOCR-007** was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency **and** urge incontinence. The study had three equally sized arms: tolterodine IR tablets 2 mg bid, tolterodine PR capsules 4 mg qd, 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. This supplement proposes major changes to the **CLINICAL STUDIES** and **ADVERSE REACTIONS** sections of the label.

While supplement **SE8-004** was being reviewed, two other Detrol supplements (**SLR-** for were being evaluated in the Division. The review team believed that it would be most efficient to review all three supplements and incorporate the changes into one revised label to be offered to the sponsor for consideration. The label with combined revisions from all three supplements was sent to the sponsor on 10/6/00.

SUMMARY OF IMPORTANT LABELING ISSUES (SE8-004, [redacted]

SE8-004 (See Review by Brenda Gierhart MD dated 10/16/00)
As mentioned above **SE8-004** is supported by data from trial 98-TOCR-007. The sponsor proposed to make extensive changes to the **CLINICAL STUDIES and ADVERSE REACTIONS** section of the Detrol label. The sponsor proposed eliminating [redacted]

The primary reviewer recommended placing data from all four trials into the label (see P. 44-49 of Dr. Gierhart's Review). I agree with the primary reviewer, that it would be most useful for providers to have information from all four placebo controlled trials as proposed by the Division.

The **ADVERSE REACTIONS** section of the currently approved label contains an extensive table entitled "Incidence (%) of Adverse Events Reported in ≥**1%** of Patients Treated with DETROL (2 mg bid) in 12-week, Phase 3 Clinical Studies". The sponsor proposes to markedly change this table by: [redacted]

The sponsor's rationale making these changes was "to be consistent with labeling presentations for other drugs in this class"

Recognizing the need to fairly represent information contained in the **ADVERSE REACTIONS** section, an alternative to the sponsor's proposed label (see page 49-54 of Dr. Gierhart's review) was proposed. Dr. Gierhart's proposal was based on thoughtful consideration of communicating the appropriate information to prescribers and information provided in the Draft Guidance for Industry, recently submitted for public comment, entitled "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics"(see page 39-40 Dr Gierhart's review). I agree with the primary clinical reviewer's labeling comments for this section. I also agreed with other minor changes proposed in this submission by the primary clinical, biopharmaceutics and chemistry reviewers.

[redacted]

OTHER REVISIONS (unrelated to a particular supplement)

[redacted]

ADDENDUM

Biopharmaceutics will convey a question to the sponsor regarding dosing recommendations for renally impaired patients in the latest version of the label which will be attached to the approvable letter.

DSI inspections were completed for two of three clinical study sites and results were found to be acceptable. Information from Dr. Sheldon Freedman's site requested by DSI in order to complete their inspection was not received as of October 23, 2000.

Recommendation: I agree with the primary reviewers of all disciplines and support the proposed recommended changes in the label as conveyed to the sponsor on 10/6/00. As of 10/20/00 comments on the divisions recommended labeling changes were not received from the sponsor. In a tcon with the sponsor on 10/19/00, the sponsor stated that they wished to continue further labeling negotiations. Therefore an approvable action will be taken at this time pending finalized labeling and successful completion of the DSI inspection of Dr. Freedman's study site.

ATTACHMENTS

/S/

Daniel A. Shames MD
Acting Deputy Director, DRUDP

Memorandum

To:	**NDA 20-771**
Through:	Dan Shames, M.D. Deputy Director, HFD-580
From:	Brenda S. Gierhart, M.D. Medical Officer, HFD-580
Date:	April 4, 2001
Re:	**SE8-004** Detrol™ (tolterodine tartrate tablets) Pharmacia & Upjohn MO Review of Division of Drug Marketing, Advertising and Communications Comments (dated April 3, 2001)

Three Detrol labeling comments were submitted by Barbara Chong, Pharm. D., BCPS, Division of Drug Marketing, Advertising and Communications (DDMAC) to HFD-580, Division of Reproductive and Urologic Drug Products (DRUDP) on April 3, 2001 and are summarized as follows:

1) The word "pronounced" in the **CLINICAL PHARMACOLOGY** section seems promotional in tone
2) Grammatical error in ***Absorption*** subsection with first sentence reading "In a study with of 14C..."
3) Request to change the word "lowered" to [redacted] in the **DOSAGE AND ADMINISTRATION** section regarding Detrol Tablet 2 mg tablets

The three comments have been reviewed.

Reviewer's comments:

1) **It is acceptable to use the word "pronounced" in the CLINICAL PHARMACOLOGY section, third paragraph, first sentence which reads: Tolterodine has a pronounced effect on bladder function in healthy volunteers. The word "pronounced" is defined as "decided" or "strongly marked". The urodynamic studies in the healthy volunteers showed several "decided" effects that are listed in the second sentence. An identical sentence is in the Detrol LA CLINICAL PHARMACOLOGY sectio[redacted]**

2) **The first sentence of the CLINICAL PHARMACOLOGY section, Pharmacokinetics, *Absorption*, subsection of the final Detrol labeling to be submitted to Sponsor correctly reads "In a study with 14C..." No change is needed.**
3) **The recommended dosage is accurately stated as lowered, since it is recommended that patients begin on 2 mg twice daily and the dosage lowered to 1 mg twice daily based on individual response.[redacted]. No change is recommended.**

2 page(s) of revised draft labeling has been redacted from this portion of the review.

/s/

Brenda Gierhart
4/4/01 02:35:28 PM
MEDICAL OFFICER

Daniel A. Shames
4/4/01 04:33:41 PM
MEDICAL OFFICER

Memorandum

To:	**NDA 20-771**
Through:	Dan Shames, M.D. Deputy Director, HFD-580
From:	Brenda S. Gierhart, M.D. Medical Officer, HFD-580
Date:	April 2, 2001
Re:	**SE8-004** Detrol™ (tolterodine tartrate tablets) Pharmacia & Upjohn MO Safety Update

On October 23, 2000 an approvable action letter for NDA 20-771/S-004 was sent to the Sponsor. A complete response to the October 23, 2000 action letter (resubmission) dated October 26, 2000 to NDA 20-771/S-004 was received at the Agency on October 27, 2000. No safety information was included in the resubmission. An Annual Report had been submitted to NDA 20-771 on May 15, 2000 and Periodic Safety Reports had been sent as P010 on April 5, 2000 and P012 on July 5, 2000.

Since receiving the resubmission on October 27, 2000 the Sponsor submitted two Period Safety Reports: P013 on November 3, 2000 and P014 on January 5, 2001. Both Period Safety Reports were reviewed by the Primary Medical Officer assigned to NDA 20-771, Mark Hirsch, MD and were NAI.

Reviewer's comment:

1) **There are no new safety issues for NDA 20-771 since the approvable action letter was sent to the Sponsor on October 23, 2000.**

cc: Original NDA 20-771
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

/s/

Brenda Gierhart
4/2/01 03:10:51 PM
MEDICAL OFFICER

Daniel A. Shames
4/2/01 03:50:47 PM
MEDICAL OFFICER

Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum

To:	**NDA 20-771**
Through:	Dan Shames, M.D. Deputy Director, HFD-580 Ameeta Parekh, Ph.D. Team Leader, Division of Pharmaceutical Evaluation II
From:	Brenda S. Gierhart, M.D. Medical Officer, HFD-580 DJ Chatterjee, Ph.D. Division of Pharmaceutical Evaluation II
Date:	March 28, 2001
Re:	Detrol™ (tolterodine tartrate tablets) Pharmacia & Upjohn Correspondence Date: March 14, 2000 Date Received: March 15, 2000 **SE8-004** Detrol™ Package Insert submitted March 21, 2001

Background:

NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was 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 supplement submission for NDA 20-771 was It was dated January 12, 1999, received January 13, 1999, and proposed t

The Clinical Pharmacology and Biopharmaceutics Review by Soraya Madani, Ph. D. dated April 29, 1999 recommended that all sponsor proposed revisions be accepted except for two sentences in th On November 10, 1999, the sponsor was notified that the review o had been completed and the agency had two

Current submissions:

The sponsor did not accept these recommendations and submitted correspondence dated March 14, 2000 and received March 15, 2000 with an alternate text for the disputed three sentences and an altered sentence in th

The Clinical Pharmacology and Biopharmaceutics Review by Dhruba J. Chatterjee, Ph.D. dated August 15, 2000 and finalized on September 13, 2000 recommended revisions to all four of the sponsor proposed sentences. These revisions were incorporated into the Package Insert revisions for SE8-004.

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in [redacted]

The March 21, 2001 submission was reviewed. The sponsor has accepted all four of the revised sentences as recommended in the Clinical Pharmacology and Biopharmaceutics Review of [redacted] by Dhruba J. Chatterjee, Ph.D. dated August 15, 2000.

Reviewer's comment:

1) **The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for [redacted] as well as for SE8-004.**

Recommendation:

1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application [redacted] has been superceded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

Brenda Gierhart
3/29/01 02:53:58 PM
MEDICAL OFFICER

Dhruba Chatterjee
3/29/01 03:12:42 PM
BIOPHARMACEUTICS

Daniel A. Shames
4/2/01 04:03:46 PM
MEDICAL OFFICER

nulldate
MEDICAL OFFICER

Ameeta Parekh
4/3/01 09:17:23 AM
BIOPHARMACEUTICS
I concur.

Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum

To:	**NDA 20-771**
Through:	Dan Shames, M.D. Deputy Director, HFD-580 Ameeta Parekh, Ph.D. Team Leader, Division of Pharmaceutical Evaluation II
From:	Brenda S. Gierhart, M.D. Medical Officer, HFD-580 DJ Chatterjee, Ph.D. Division of Pharmaceutical Evaluation II
Date:	March 28, 2001
Re:	**SE8-004** (BL) Detrol™ (tolterodine tartrate tablets) Pharmacia & Upjohn MO Review of Faxed Detrol™ Package Insert Correspondence Date: March 21, 2001 Date Received: March 22, 2001

Current submission:
On March 21, 2001, the Sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in [redacted]

The submission was reviewed. The nine discrepancies discussed during the March 20, 2001 teleconference and documented in the minutes have all been corrected.

Reviewer's comment:
1) **The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable. The labeling issues pending at the date the October 23, 2000 Approvable action letter have been resolved.**

Recommendation:

1) Recommend sending an approved letter and copy of the March 20, 2001 proposed label to the Sponsor for their supplemental new drug application SE8-004, which was received December 23, 1999.

cc: Original NDA 20-771
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

Brenda Gierhart
3/29/01 02:57:55 PM
MEDICAL OFFICER

Dhruba Chatterjee
3/29/01 03:07:45 PM
BIOPHARMACEUTICS

Daniel A. Shames
4/2/01 03:58:59 PM
MEDICAL OFFICER

Ameeta Parekh
4/3/01 09:07:53 AM
BIOPHARMACEUTICS
I concur.

Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum

To: NDA 20-771

Through: Dan Shames, M.D.
Deputy Director, HFD-580

Ameeta Parekh, Ph.D.
Team Leader, Division of Pharmaceutical Evaluation II

From: Brenda S. Gierhart, M.D.
Medical Officer, HFD-580

DJ Chatterjee, Ph.D.
Division of Pharmaceutical Evaluation II

Date: March 28, 2001

Re: Detrol™ (tolterodine tartrate tablets)
Pharmacia & Upjohn
[redacted]

Correspondence Date: June 9, 2000
Date Received: June 12, 2000
SE8-004
Detrol™ Package Insert submitted March 21, 2001

Background:

NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was 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 [redacted] supplemental submission for NDA 20-771 was [redacted]). It was dated June 9, 2000 and received on June 12, 2000. It proposes [redacted] All the proposed changes were reviewed in my Medical Officer Review Memorandum dated October 6, 2001 and the recommendations incorporated into the Package Insert revisions for SE8-004.

The Clinical Pharmacology and Biopharmaceutics Review by DJ Chatterjee, Ph. D. dated September 18, 2000 and finalized on October 4, 2000 discussed the labeling changes that pertained to three clinical pharmacology issues in the Race, Renal Insufficiency and Drug Interactions subsections. The recommendations made by Dr. Chatterjee were also incorporated into the Package Insert revisions for SE8-004.

Current submission:

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in [redacted]

The March 21, 2001 submission was reviewed. The sponsor has incorporated language into the revised labeling that addresses all the issues raised in the Clinical Pharmacology and Biopharmaceutics Review of ——— by Dhruba J. Chatterjee, Ph.D. finalized on October 4, 2000 and by myself in the Medical Officer Memorandum dated October 6, 2000.

Reviewer's comment:

1) **The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for ——— , as well as for SE8-004.**

Recommendation:

1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application ——— has been superceded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

Brenda Gierhart
3/29/01 03:01:06 PM
MEDICAL OFFICER

Dhruba Chatterjee
3/29/01 03:11:19 PM
BIOPHARMACEUTICS

Daniel A. Shames
4/2/01 04:08:20 PM
MEDICAL OFFICER

Ameeta Parekh
4/3/01 09:48:28 AM
BIOPHARMACEUTICS
I concur.

Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum

To:	**NDA 20-771**
Through:	Dan Shames, M.D. Deputy Director, HFD-580 Ameeta Parekh, Ph.D. Team Leader, Division of Pharmaceutical Evaluation II
From:	Brenda S. Gierhart, M.D. Medical Officer, HFD-580 DJ Chatterjee, Ph.D. Division of Pharmaceutical Evaluation II
Date:	March 28, 2001
Re:	Detrol™ (tolterodine tartrate tablets) Pharmacia & Upjohn Correspondence Date: October 5, 2000 Date Received: October 6, 2000 **SE8-004** Detrol™ Package Insert submitted March 21, 2001

Background:
NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was 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.

Current submissions:
The [redacted] supplemental submission for NDA 20-771 was [redacted] Revision)-Changes Being Effected. It was dated October 5. 2000 and was received on October 6, 2000. It stated tha[redacted] All nine changes were reviewed and the acceptable wording was incorporated into the Package Insert revisions for SE8-004.

The specific changes were as follows:

- **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, *Gender*** subsection: the proposed change of the units from µg/L to µg·h/L was acceptable and was incorporated into the Package Insert revisions for SE8-004.

- **PRECAUTIONS,** [redacted] The original subsection title was retained into the Package Insert revisions for SE8-004.

- **PRECAUTIONS, Information for Patients** subsection: the proposed inclusion of dizziness and drowsiness was acceptable and was incorporated into the Package Insert revisions for SE8-004.

- **PRECAUTIONS, Pregnancy** subsection: the proposed change from [redacted] was not acceptable. The alternative change to "be embryolethal" was acceptable and was incorporated into the Package Insert revisions for SE8-004.

- **ADVERSE REACTIONS** and **OVERDOSAGE** sections: the proposed addition of "Tablets" after the first mention of DETROL was acceptable and was incorporated into the Package Insert revisions for SE8-004.

- **ADVERSE REACTIONS** section: the proposed change of [redacted] was no longer relevant due to the changes to this section in SE8-004 which included eliminating this sentence.

- **ADVERSE REACTIONS** section: the proposed change of [redacted] in the Adverse Events Incidence table was not acceptable. The WHOART term for dry eyes is xerophthalmia. Xerophthalmia was retained in the Package Insert revisions for SE8-004 in the Adverse Events Incidence table.

- **ADVERSE REACTIONS** section: the proposed change of adding [redacted] after the adverse event table was not acceptable. The proposed change was not incorporated into the Package Insert revisions for SE8-004.

- **ADVERSE REACTIONS, Postmarketing Surveillance** subsection: the proposed addition of the subsection and the sentence "The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, tachycardia, peripheral edema." was acceptable and was incorporated into the Package Insert revisions for SE8-004.

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile 1on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in [redacted]

The March 21, 2001 submission was reviewed. The sponsor has incorporated language into the revised labeling that addresses all the issues raised in [redacted]

Reviewer's comment:

1) The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for [redacted] as well as for SE8-004.

Recommendation:

1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application [redacted] has been superceded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

Brenda Gierhart
3/29/01 03:04:24 PM
MEDICAL OFFICER

Dhruba Chatterjee
3/29/01 03:10:01 PM
BIOPHARMACEUTICS

Daniel A. Shames
4/2/01 04:06:18 PM
MEDICAL OFFICER

Ameeta Parekh
4/3/01 09:24:50 AM
BIOPHARMACEUTICS
I concur.

MEMORANDUM

To:	NDA 20-771 S-004
Through:	Dan Shames, MD Deputy Director, HFD-580
From:	Brenda S. Gierhart, MD Medical Officer, HFD-580
Date:	March 6, 2001
Re:	Resubmission to NDA 20-771 Efficacy Supplement S-004 Correspondence Date: February 27, 2001 Date Received: February 28, 2001 PDUFA Date: April 27, 2001

Current submission:
Pharmacia & Upjohn has submitted a revised Detrol™ label, dated February 26, 2001. This submission is in response to the Division draft label, dated February 12, 2001, which was faxed to the Sponsor on February 15, 2001. The Sponsor has also provided four attachments:

- Attachment #1 is provided in support of their proposed changes to Table 2
- Attachment #2, 3, & 4 are provided in support of their proposed modification to two numerical values in Table 3 and to one sentence in the Adverse Reactions section. The sentence discusses the expected side effects of antimuscarinic agents.

There are a total of nine MARKED proposed revisions. The Sponsor made additional changes to the label that were NOT marked as revisions. All revisions/changes made will be discussed in the order they occur in the draft label.

Unmarked Changes #1 (pg. 1) **DESCRIPTION** section; second sentence; the Sponsor

Reviewer's comment:

1) **This revision is not acceptable per review by Dr. David Lin, Chemistry. The Sponsor should return the**

Unmarked Changes #2 (pg. 2) **CLINICAL PHARMACOLOGY Pharmacokinetics** ***Absorption*** section; first sentence; the Sponsor changed

Reviewer's comment:

2) **This revision is not acceptable. The Sponsor should first sentence, to be consistent with the Detrol LA label.**

Marked Revision #1 (pg. 4) **CLINICAL PHARMACOLOGY Pharmacokinetics in Special Populations *Renal Insufficiency*** section; third sentence; proposes to change the word "subjects" to "volunteers" for consistency within that section.
Reviewer's comment:
3) This revision is acceptable.

Marked Revision #2 (pg. 6) **CLINICAL STUDIES** section; second and third paragraphs; proposes to reverse the order of the studies when discussing the efficacy endpoints. The Sponsor wishes to first present the efficacy endpoints for study 007 and then follow with the sentence discussing the efficacy endpoints for studies 008, 009, and 010.
Reviewer's comment:
1) This change is acceptable if the order of the efficacy endpoints is changed and the location of the words "Table 3" is changed. The number of incontinence episodes per week should become the new first bullet, since it was the primary efficacy endpoint for study 007. The location of the words "Table 3" should be changed to be consistent with the location of "Table 2" in the first sentence.

Unmarked Changes #3 and Marked Revision #3 (pg. 7) **CLINICAL STUDIES** section **Table 2.**;
The Sponsor made several changes to Table 2, which were NOT marked as changes including:
- "2 mg bid" was added to the second column title
- [redacted] ' was deleted from the fourth column title
- the location of numbers were moved in the fourth column to align with the row "Mean Baseline"
- the number alignment in the second, third, and fourth columns were changed from left alignment to centered alignment
- — was removed six times in the second and third columns

In addition to the above changes, the Sponsor proposes to add "SD" to the second and third column titles, and insert corrected SD values into the row labeled "Number of incontinence episodes/week".
Reviewer's comment:
1) The Sponsor wishes to revise Table 2's format to make it consistent with Table 3's format. This is acceptable. To accomplish this, several changes are necessary, which have been made in the attached revised label.

Unmarked Changes #4 (pg. 8) **CLINICAL STUDIES** section **Table 3.**;
The Sponsor made several changes to Table 3, which were NOT marked as changes including:
- in final column, asterisk was moved from after to before difference
- alignment was changed for columns with numbers from left alignment to centered alignment

Reviewer's comment:

1) **The Sponsor wishes to revise Table 2's format to make it consistent with Table 3. To do this, several changes are necessary, which have been made in the attached revised label.**

Revision #4 (pg. 9) **PRECAUTIONS General** ***Risk of Urinary Retention and Gastric Retention*** section, first sentence; the word "Tablets" was added after DETROL. The Sponsor noted that this was in accordance to good company trademark practices (i.e. first mention in each major section).

Reviewer's comment:

1) **This revision is acceptable.**

Unmarked Change #4 (pg. 10) **PRECAUTIONS Pregnancy** section, between third and fourth sentences; a

Reviewer's comment:

2) **This revision is not acceptable. The Sponsor is to delet**

Revision #5 (pg. 11) **ADVERSE REACTIONS** section, third paragraph, final sentence; the Sponsor wishes to change the sentence from:

Reviewer's comment:

1) **This revision is not acceptable. The original sentence should be retained.**

Revision #6 (pg. 12) **ADVERSE REACTIONS** section, Table 4; the Sponsor has changed the percentages of Detrol patients with dyspepsia to 4 % and the percentage of placebo patients with dyspepsia to 1%.

Reviewer's comment:

1) **This revision is acceptable.**

Revision #7 (pg. 12) **ADVERSE REACTIONS** Postmarketing Surveillance section, first sentence; the Sponsor has changed the sentence from:

Reviewer's comment:

1) **This revision is not acceptable.** Acceptable wording would be to retain the original sentence and add the new second sentence "Because the following are spontaneously

reported events from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

Revision #8 (pg. 13) **OVERDOSAGE Management of Overdosage** section, second paragraph, final sentence; the words "of tolterodine" was deleted as an editorial change.
Reviewer's comment:
1) **This revision is acceptable.**

Revision #9 (pg. 13) **DOSAGE AND ADMINSTRATION** section, first sentence; the word "Tablets" was added after DETROL. The Sponsor noted that this was in accordance to good company trademark practices (i.e. first mention in each major section).
Reviewer's comment:
1) **This revision is acceptable.**

Recommendation:
1) Attachment #1 should be sent to the Sponsor. Attachment #1 is DRUDP's response (3/2/01) to Pharmacia's proposed changes (2/26/01) to the Detrol Package Insert. It should be noted that additions to Pharmacia's 10/25/00 Detrol Package Insert are marked as double underlining, deletions are marked as strikethroughs, and comments to the Sponsor are marked as bracketed, bolded, and in italics.
2) If the Sponsor accepts Attachment #1, an approved action for NDA 20-771 SE8-004 is anticipated by March 12, 2001.

cc: Original NDA 20-771
HFD-580: Division File
HFD-580: S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

Attachment #1:

Detrol™
tolterodine tartrate
tablets

13 page(s) of revised draft labeling has been redacted from this portion of the review.

/s/

Brenda Gierhart
3/6/01 03:02:30 PM
MEDICAL OFFICER

Daniel A. Shames
3/9/01 02:36:17 PM
MEDICAL OFFICER

Farinas

AUG 31 2000

MEMORANDUM

To: IND 56,406 Tolterodine Prolonged Release
NDA 20-771 Tolterodine Immediate Release
NDA 21-228 Tolterodine Prolonged Rele (S)

Through: Dan Shames, MD
Acting Deputy Director, HFD

From: Brenda S. Gierhart, MD (S) 8/31/00
Medical Officer, HFD-580

Date: August 31, 2000

Re: Submission N040 PC
Submitted August 21, 2000
Received August 22, 2000
Omitted Submission of Protocol Amendment

Current submission:
DRUDP recently notified Sponsor of the omitted submission of Protocol 98-TOCR-007 Amendment #4 issued on July 2, 1999. Sponsor now submits Amendment #4 which:

- Added five centers in the Russian Federation and Ukraine.
- Replaced the t-test with an ANOVA analysis with treatment, center, and treatment by country as factors.
- Deleted King's Health Questionnaire completion for subjects in the Russian Federation or Ukraine, since it is not available in Russian.
- Added subgroup analyses on micturition variables with respect to sex and races.
- Added the sentence "If micturition chart diaries are not completed according to the protocol, the estimation of the micturition variable will be based on the available data" to the analysis plan for the Intention-to-treat population.

Per Sponsor, the statistical and analytical plans were changed in response to suggestions from the FDA.

Reviewer's comments:

1) **It is unclear exactly how and why the micturition variables in the ITT population would be estimated. The Sponsor should clarify what was meant by "estimation", how the estimations were performed, and provide a list of subjects who had their micturition chart diary data estimated.**

Recommendation:

The Sponsor should be called or sent a brief regulatory letter with the following requests for information:

1) Please clarify what was meant by the term "estimations" as used in Protocol 98-TOCR-007, Protocol Amendment #4, 10 STATISTICS, 1.Intention-to treat population.
2) Describe how the estimations were performed.
3) Please provide list of subjects who had their micturition chart diary data estimated.

cc: Original IND 56,406
Original NDA 20-771
Original NDA 21-228
HFD-580 Division File
S. Allen, D. Shames, B. Gierhart, E. Farinas, HFD-580

Teleconference Minutes

Date: March 20, 2001 **Time:** 8:30-9:00 AM, EDT **Location:** Parklawn; 17B-43

NDA 20-771/S-004 **Drug:** Detrol (tolterodine tartrate) tablets **Indication:** overactive bladder

Sponsor: Pharmacia & Upjohn Company

Type of Meeting: Clarification

Meeting Chair: Brenda Gierhart, M.D., Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Mark Mannebach, Ph.D. – Associate Director, Global Regulatory Affairs

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

FDA Attendees:
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participant:
Mark Mannebach, Ph.D. – Associate Director, Global Regulatory Affairs, Pharmacia & Upjohn Company
Dora Cohen – Pharmacia & Upjohn Company

Meeting Objective: To convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 S004, (faxed on March 9, 2001 to the sponsor) and that received from the sponsor via facsimile on March 15, 2001.

Background: On March 9, 2001, DRUDP sent the sponsor a proposed version of the label for NDA 20-771/S-004, which included comments from DRUDP reviewers. This proposed label was sent via electronic mail as well as via facsimile. The sponsor submitted a response via facsimile on March 15, 2001, accepting the March 9, 2001, FDA label recommendations. It was noted that the wording in the version attached to the March 15, 2001, facsimile did not agree with the wording in the FDA March 9, 2001, proposal.

Discussion:

- the sponsor was notified that the proposed label addressed the label changes proposed in —, S-004, —
- the sponsor was notified of discrepancies noted in the March 15, 2001 facsimile, and also of additional information and corrections which should be incorporated into the label; the discrepancies and additional information are:
  - a bracket should be added immediately before "bis" in the chemical name, in the second sentence under the **DESCRIPTION** section

- the spelling should be corrected in the third sentence under the **Renal Insufficiency** subsection to correctly read "N-dealkylated"
- the wording should be changed from "N-dealkylated olterodine" to "N-dealkylated hydroxylated tolterodine" in the third sentence under the **Renal Insufficiency** subsection
- in Table 2, under the **CLINICAL STUDIES**, in the first section "Number of Incontinence Episodes per Week" the word "Week" was capitalized, and in the same table the decimal alignment was not maintained throughout the table; however, the Division does not object to capitalizing the word "Week" in the table, and if it is not technically possible to maintain the decimal alignment, the Division will accept the format of Table 2 as listed in the March 15, 2001 facsimile
- in Table 3, under the **CLINICAL STUDIES** section, the figure "93" has been omitted as the first entry under the "Detrol" column, in the "008 Number of patients" line; the decimal alignment was not maintained throughout the table; and the asterisks in the first, fourth, fifth, seventh, eighth, and ninth entry under the "Difference" column were not placed between the figure and the parenthesis
- in the **Pregnancy** subsection, under the **PRECAUTIONS** section, a new paragraph was created incorrectly between the second and third sentence
- in the fifth paragraph under the **ADVERSE REACTIONS** section, an unnecessary comma was introduced between the words "dizziness" and "and" in the last sentence of this paragraph
- in Table 4, under the **ADVERSE EVENTS** section, the width of the margins in the last two was increased; if it is not technically possible to decrease the width of these columns, the Division will accept the format of Table 4 as listed in the March 15, 2001, facsimile
- the date of last printing (i.e. March 2001) had a strike over under the **HOW SUPPLIED** section

- the sponsor indicated that a revised label will be sent correcting the errors noted and including the additional information and revisions provided today

Decisions made:

- the sponsor agreed to amend the March 15, 2001, proposed label to conform with the changes discussed in today's teleconference

Action Items:

- DRUDP will send via facsimile and e-mail the revised FDA proposed label for Supplement 004 *(revised version sent to the sponsor via facsimile on March 20, 2001)*
- the sponsor will send via e-mail as soon as possible their response to the March 20, 2001, proposed FDA label *(response received electronically on March 20, 2001)*

Minutes Preparer **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.

cc:
Original IND
HFD-580/DivFile
HFD-580/Allen/Shames/Hirsch/Gierhart/Rumble/Farinas

drafted: erf/3.20.01
concurrence: Rumble 3.20.01/Gierhart 3.20.01
final: erf/3.22.01

MEETING MINUTES

/s/

Evelyn Farinas
3/22/01 11:40:10 AM
CSO

tcon march 20 label revisions

Brenda Gierhart
3/22/01 11:47:10 AM
MEDICAL OFFICER

42 page(s) of revised draft labeling has been redacted from this portion of the review.

Teleconference Minutes

Date: October 19, 2000	**Time:** 1:45-2:00 PM, EDT	**Location:** Parklawn; 17B-45
NDA 20-771/S-004	**Drug:** Detrol (tolterodine tartrate)	**Indication:** overactive bladder
Sponsor:	Pharmacia & Upjohn Corporation	
Type of Meeting:	Clarification	
Meeting Chair:	Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)	
External Lead:	Gregory Shawaryn, Regulatory Manager, Regulatory Affairs	
Meeting Recorder:	Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager	

FDA Attendees:
Daniel Shames, M.D. - Acting Deputy Director, DRUDP (HFD-580)
Evelyn R. Farinas, RPh, M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Gregory Shawaryn - Regulatory Manager, Regulatory Affairs
Mark Mannavath – Regulatory Affairs

Meeting Objective: To communicate to the sponsor the status of Supplement 004 review.

Background: Sponsor submitted an efficacy supplement (S-004) to NDA 20-771 for tolterodine immediate release formulation, on December 22, 1999. This labeling supplement requires review of clinical data (Study Report 98-TOCR-007). In this study, the sponsor plans to demonstrate a statistically significant decrease in the number of incontinent episodes with tolterodine treatment compared with placebo. The 10-month goal date for this submission is October 23, 2000.

Discussion:
- the sponsor will most likely receive an Approvable letter for Supplement 004 for NDA 20-77, because labeling discussions for Supplement 004 between DRUDP and Pharmacia & Upjohn will not be finalized prior to the 10-month goal date of October 23, 2000
- the intent of DRUDP is to craft a label that addresses Supplements – and 004 for NDA 20-771, as well as the pending NDA 21-228 for the tolterodine extended release product
- the time frame for labeling discussions should accommodate both parties; DRUDP's intent is to provide a response within four weeks after receipt of the sponsor's revisions
- the sponsor should submit the rationale for their preferred name for the extended release product, (i.e. Detrol XL); the final decision for an approved name for this product rests with DRUDP

Decisions made:
- DRUDP will probably send an Action letter to the sponsor on October 23, 2000
- the sponsor will submit rationale for the preferred name for the extended release product

Action Items:

- minutes of this teleconference will be faxed to sponsor with

/S/

/S/

Minutes Preparer

Concurrence, Chair 10/20/00

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.

cc:
Original IND
HFD-580/DivFile
HFD-580/Allen/Shames/Rumble/Farinas

drafted: erf/10.20.00
concurrence: Shames 10.20.00/Colangelo for TR 10.20.00
final: erf/10.20.00

MEETING MINUTES

Labeling/Status Meeting Minutes

Date: October 16, 2000 Time: 2:00-3:00 PM, EST Location: PKLN; 17B43

NDA 20-771/S-004 Drug: Detrol Indication: overactive bladder

Sponsor: Pharmacia & Upjohn Corporation

Type of Meeting: Status/Labeling discussion

Meeting Chair: Brenda Gierhart, M.D., Medical Officer, 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:
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
David Lin, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss status of this NDA and label revisions to the sponsor's proposed label in supplement — S-004, and —.

Background: Pharmacia & Upjohn Corporation has submitted to DRUDP several label supplements, —, S-004 (December 22, 1999) and — for tolterodine immediate release tablets. In — the sponsor proposed changes — section, and to the — section of the label. In this supplement, the sponsor provided literature data and — to support the proposed changes. In S-004 the sponsor proposed changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES and ADVERSE REACTIONS sections. In support of the changes for the first two sections, the sponsor did not submit any new data, and referred to the Original NDA (Item 6); for the remaining two sections, the sponsor submitted Protocol 98-TOCR-007 as supporting documentation. In —, the sponsor

—

—

—s. No references were provided in support of the changes to the other sections. DRUDP's revised version of the proposed label was faxed to the sponsor on September 29, 2000. The same label was refaxed on October 3, 2000, when the sponsor indicated that it had not been received.

Discussion:

- An Approvable action pending resolution of the label is being considered for this application
- Sponsor indicated via telephone conversation on October 16, 2000 between Ms. Farinas and Mr. Shawaryn, that DRUDP's proposed label revisions were being discussed internally, but that additional discussions were still required; sponsor did not indicate a specific time-frame for submitting their response to the DRUDP's revised label; Mr. Shawaryn indicated that Pharmacia & Upjohn was not aware that this application was on a 10-month clock
- DSI report is pending; Dr. Roy Blay has been notified
- Chemistry review is pending; Dr. David Lin is finalizing this report *(final review submitted October 16, 2000)*
- Statistics report is pending; Dr. David Hoberman indicated previously that information necessary for review had not been submitted by the sponsor, despite his request (*sponsor was asked to submit another set of statistic data via overnight delivery; diskette received October 17, 2000 and delivered to Dr. Hoberman)*

Action Items:

- Call Dr. Blay for an update on receipt of DSI report *(draft copy sent electronically on October 16, 2000)*
- Contact Dr. Hoberman for status of Statistics review
- Review Action Package for completeness

/S/ _____ /S/

Minutes Preparer Concurrence, Chair

Cc:

IND Arch:
HFD-580/Div File
HFD-580/Allen/Shames/Hirsch/Gierhart/Rhee/Lin/Rumble

Drafted: October 18, 2000
Concurrence: Gierhart 10.18/00/Lin 10.18.00/Rumble
Finalized: 10.19.00

MEETING MINUTES

Labeling Meeting Minutes

Date: September 18, 2000 Time: 2:00-3:00 PM, EST Location: PKLN; 17B43

NDA 20-771/S-004 Drug: Detrol Indication: overactive bladder

Sponsor: Pharmacia & Upjohn Corporation

Type of Meeting: Status/Labeling discussion

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)
David Lin, Ph.D. – Chemistry Reviewer, @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Clinical Pharmacology and Biopharmaceutics Team Leader, @ DRUDP (HFD-580)
D.J. Chatterjee, Ph.D. - Clinical Pharmacology and Biopharmaceutics Reviewer, @ DRUDP (HFD-580)
Barbara Chong – Reviewer, DDMAC
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss label revisions to the sponsor's proposed label in supplements [redacted], S-004, and [redacted]

Background: Pharmacia & Upjohn Corporation has submitted to DRUDP several label supplements, [redacted], S-004 (December 22, 1999) and S-[redacted] for tolterodine immediate release tablets. In [redacted], the sponsor proposed changes to the [redacted]s. In S-004 the sponsor proposed changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES and ADVERSE REACTIONS sections. In support of the changes for the first two sections, the sponsor did not submit any new data, and referred to the Original NDA (Item 6); for the remaining two sections, the sponsor submitted Protocol 98-TOCR-007 as supporting documentation. In [redacted], the sponsor proposed changes to [redacted] section changes. No references were provided in support of the changes to the other sections.

Discussion:

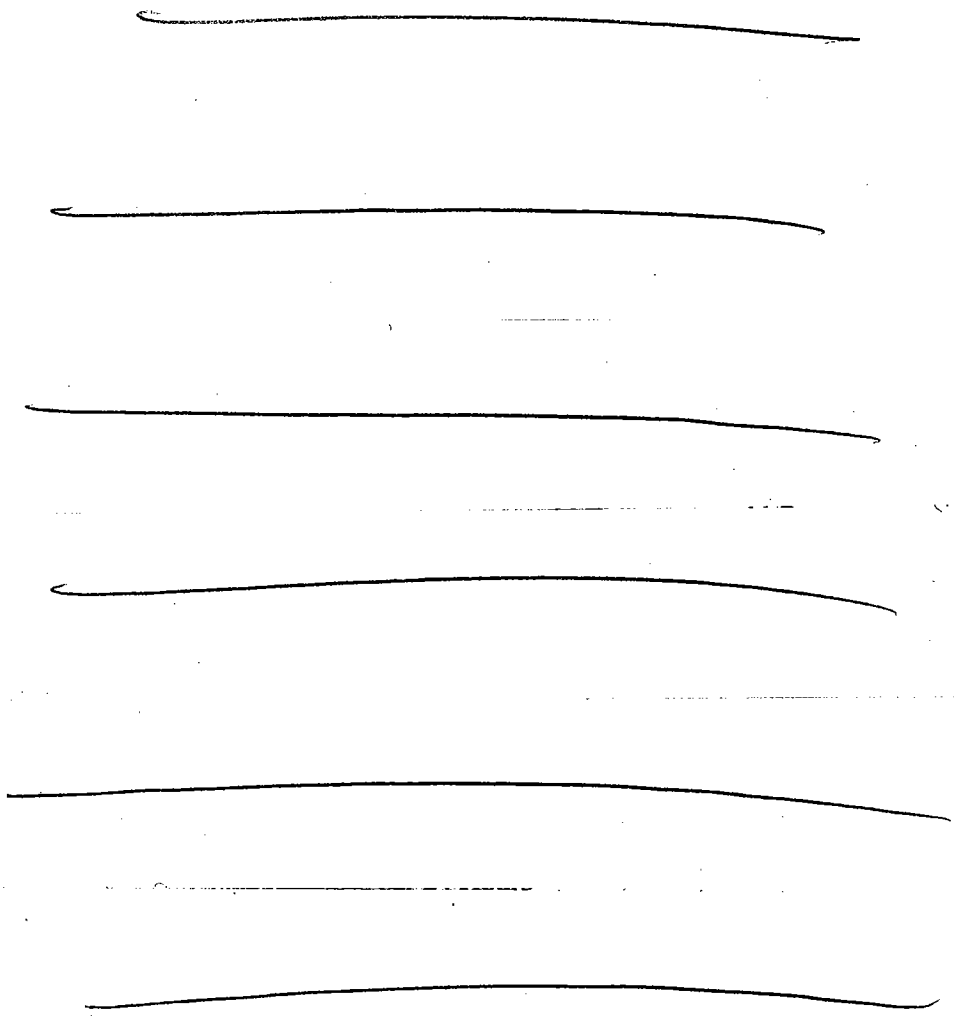
Comments and recommendations to the sponsor's proposed label, per section, were:

- DESCRIPTION:
  - approve the addition of these three sentences proposed i[redacted] "The pKa value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3."
- HOW SUPPLIED:
  - change existing storage statement to "store at 25° C (77° F); excursion permitted to...."
  - ask the sponsor to make this change to all their carton labels; the sponsor may use existing supply of carton labels before implementing changes
- CLINICAL PHARMACOLOGY:
  - the changes proposed in [redacted] to the third paragraph [redacted]) are unacceptable as written. Alternative wording will be sent to the sponsor.
- Pharmacokinetics in Special Population:
  - the concepts proposed in [redacted] are acceptable
  - further language revisions are necessary to the sponsor's proposed language ([redacted]
- Drug-Drug Interactions:
  - the concepts proposed in [redacted] are acceptable
  - further language revisions are necessary to the sponsor's proposed language in [redacted]
  - the concepts proposed in [redacted] are acceptable
  - the following exact text should be inserted in the label to address th [redacted] roposal:
- Clinical Studies:

- proposed language and tables should be changed to "DETROL Tablets were evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in four placebo-controlled, 12-week studies. A total of 853 patients received DETROL 2 mg twice daily and 685 patients received placebo. The majority of patients were Caucasian (95%), female (78%), and with a mean age of 60 years (range, 19 to 93 years). At study entry, nearly all patients perceived they had urgency and most patients had increased frequency of micturitions and urge incontinence. These characteristics were well balanced across treatment groups for the studies. The efficacy endpoints for studies 008, 009, and 010 included the change from baseline for:

- Number of micturitions per 24 hours (averaged over 7 days)
- Number of incontinence episodes per 24 hours (averaged over 7 days)
- Volume of urine voided per micturition (averaged over 2 days)

The efficacy endpoints for study 007 were identical to the above endpoints with the exception that the number of incontinence episodes was per week. Efficacy results for the four placebo-controlled, 12-week studies are presented in the following figure:



- INDICATIONS AND USAGE:

- PRECAUTIONS
  - General subsection: same comments as in Pharmacokinetics in Special Population section (see above)
  - Drug Interactions subsection: same comments as in Drug-Drug Interactions section (see above)
-

- ADVERSE REACTIONS
  - reject the sponsor's proposed language for this section in S-004

- the language in this section should be changed to: The Phase 2 and 3 clinical trial program for DETROL Tablets included 3071 patients who were treated with DETROL (N=2133) or placebo (N=938). The patients were treated with ——— for up to 12 months. No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism.
The data described below reflect exposure to DETROL 2 mg bid in 986 patients and to placebo in 683 patients exposed for 12 weeks in five Phase 3 controlled clinical studies. Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.
— of patients receiving DETROL 2 mg bid reported adverse events versus 56% of placebo patients. The most common adverse events reported by patients receiving DETROL were dry mouth, headache, constipation, vertigo/dizziness, and abdominal pain. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are expected side effects of antimuscarinic agents.
Dry mouth was the most frequently reported adverse event for patients treated with DETROL 2 mg bid in the Phase 3 clinical studies, occurring in 34.8% of patients treated with DETROL and 9.8% of placebo-treated patients; 1.0% of patients treated with DETROL discontinued treatment due to dry mouth.
The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. 7% of patients treated with DETROL 2 mg bid discontinued treatment due to adverse events versus 6% of placebo patients; the most common adverse events leading to discontinuation were dizziness and headache.
Three percent of patients treated with DETROL 2 mg bid reported a serious adverse event versus 4% of placebo patients. Significant — changes in QT and QT_c have not been demonstrated in clinical study patients treated with Detrol 2 mg bid. The following table lists the adverse events reported in 1% or more of the patients treated with DETROL 2 mg bid in the 12-week studies. The adverse events are reported regardless of causality.

Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in >1% of Patients Treated with DETROL (2 mg bid) in 12-Week, Phase 3 Clinical Studies

Body System	Adverse Event	% DETROL 2 mg bid N=986	% Placebo N=683
Autonomic Nervous	Accommodation abnormal	2	1
	dry mouth	35	10
General	chest pain	2	1
	fatigue	4	3
	Headache	7	5
	Influenza-like symptoms	3	2
Central/Peripheral Nervous	Vertigo/dizziness	5	3

Gastrointestinal	Abdominal pain	5	3
	Constipation	7	4
	Diarrhea	4	3
	Dyspepsia	[redacted]	
Urinary	Dysuria	2	1
Skin/Appendages	skin dry	1	0
Musculoskeletal	Arthralgia	2	1
Vision	Xerophthalmia	3	2
Psychiatric	Somnolence	3	2
Metabolic/Nutritional	weight gain	1	0
Resistance Mechanism	Infection	1	0
* in nearest integer			

- OVERDOSAGE/MANAGEMENT OF OVERDOSAGE

[redacted]

  - no change should be made in the current wording of this section

- DOSAGE AND ADMINISTRATION
  - the following exact text for the third sentence of this section should be: [redacted]

Chemistry comments:
- review to be finalized within two weeks of this meeting

Biopharmaceutics comments:
- review to be finalized within two week of this meeting

Action Items:
- a single label revision with DRUDP's recommendations for [redacted], S-004 and [redacted] will be sent to the sponsor for discussion prior to the October 23, 2000, goal date
- additional comments from the Statistical reviewer will be requested by the Medical Officer and incorporated into label recommendations prior to sending DRUDP's revisions to the sponsor (*Medical officer conveyed request to Dr. Hoberman)*

(S)
Minutes Preparer

(S)
Concurrence, Chair

cc:
IND Arch:
HFD-580/DivFile
HFD-580/ Allen/Shames/Gierhart/Hoberman/ Parekh/Chatterjee/Lin/Rumble
drafted: Farinas, 9.19.00
concurrence: Shames 9.21.00/Gierhart 9.22.00/Parekh/Chatterjee/Lin/Rumble 9.20.00
final: Farinas, 10.17.00
MEETING MINUTES

ADDENDUM: October 20, 2000

Dr. Barbara Chong confirmed via e-mail that at the September 18, 2000 status meeting she recommended that the following sentence from the Clinical Pharmacology section be deleted from the labeling:

Evelyn R. Farinas

Daniel Shames

10/20/00

Gierhart

Meeting Minutes

Date: August 11, 2000 **Time:** 9:00-9:30 EST **Location: Parklawn; 17B43**

NDA 20-771/S-004 **Drug:** tolterodine **Indication:** overactive bladder

Sponsor: Pharmacia & Upjohn

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, DRUDP (HFD-580)

FDA Attendees:
Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, 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. Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manger, DURDP (HFD-580)

Meeting Objective: To discuss status of review.

Background: Sponsor submitted an efficacy supplement (S-004) to NDA 20-771 for tolterodine immediate release formulation, on December 22, 1999. This labeling supplement is coded as an SE8 which requires review of clinical data (Study Report 98-TOCR-007). In this study, the sponsor plans to demonstrate a statistically significant decrease in the number of incontinent episodes with tolterodine treatment compared with placebo. The goal date for this submission is October 23, 2000.

Discussion:
Biopharmaceutics:
- no issues
- background material will be obtained by the Medical Officer (Dr. Gierhart) and reviewed by the Biopharmaceutics Reviewer (Dr. Chatterjee) to assess the adequacy of the sponsor's proposal for additional wording to the clinical Pharmacology section of the label

Clinical:
- adequacy of proposed tables
  - statistical review is needed to determine adequacy of the proposed tables
  - submitted table format suggests greater safety of tolterodine; as proposed, the adverse events text does not adequately address the frequency of adverse events nor the placebo information
  - submission of tables which are similar and consistent with previously approved labeling may be recommended
- adverse event section

- draft adverse event guidance document is not clear
- standardization of the adverse events section of the labeling for incontinence products should be pursued
- will consult DDMAC as to which form of reporting adverse events, i.e. specific adverse events listing versus body system listing, is preferred

- multiplicity of supplements, i.e. S-004, S-006,
  - concurrent review of all labeling supplement is recommended

Chemistry:

- chemistry reviewer (Dr. Lin) will be asked to comment on the proposed addition of three sentences to the Description section describing the physical chemistry for tolterodine

Action Items:

- contact Dr. Lisa Kammerman (statistician) for review and comments on adequacy of tables
- contact Nancy Ostrove (DDMAC) for review and comments on preferred Adverse Event section format
- investigate possibility of exchanging label comments with sponsor in electronic format, via diskettes

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
NDA Arch: 20-771
HFD-580/DivFile

HFD-580/ Allen/Mann/Shames/Gierhart/Kammerman/Lin/Rhee/ Parekh/Chatterjeee/Rumble

drafted: Farinas, 8.14.00
concurrence: Shames 8.23.00/Gierhart 8.16.00/Parekh/Chatterjee 8.16.00/Rumble (KC) 8.15.00
final: Farinas, 8.23.00

filename: NDA 20771 S004 status meeting Aug.doc
MEETING MINUTES

FARINAS

Meeting Minutes

Date: February 7, 2000 **Time:** 3:10 PM, EST **Location:** Parklawn; 17B-45

NDA 20-771/S-004 **Drug:** Detrol (tolterodine immediate release)

Indication: urinary incontinence

Sponsor: Pharmacia & Upjohn

Type of Meeting: Filing meeting

Meeting Chair: Daniel Shames, MD – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

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

Meeting Objective: To discuss fileability of NDA 20-771/S-004.

Background: This efficacy supplement (S-004) was submitted on December 22, 1999. The sponsor indicated that study results demonstrate a highly statistically significant difference between Detrol (tolterodine tartrate tablets) and placebo for improvement in incontinence episodes with Detrol. Study results also showed statistically significant improvement in secondary efficacy variables, number of micturitions and mean volume voided. The sponsor is proposing a labeling update of the Clinical Studies and Adverse Reactions sections based on these data. DRUDP held a virtual filing meeting (via e-mail) on February 7, 2000 to determine if this supplement was fileable.

Discussion:
- e-mail sent to D. Shames, M. Hirsch, A. Jordan, A. Parekh, S. Madani, M.J.Rhee and D. Lin on February 7, 2000, requesting that fileability issues be identified
- the reviewers did not indicate that there were any issues which would prevent filing this supplement

Decisions reached:

- Supplement 004 is fileable

Action Items:

- none

/S/ /S/

Minutes Preparer **Concurrence, Chair**

cc:
NDA Arch:
HFD-580/DivFile

HFD-580/Allen/Mann/Shames/Hirsch/Gierhart/Jordan/Rhee/Lin/Parekh/Rumble/Farinas

drafted: Farinas 3.28.00
concurrence: Shames 4.11.00/Hirsch 3.30.00/Jordan 4.10.00/Parekh 4.12.00
/Madani/Rhee 4.12.00/Lin 3.30.00/Rumble 3.29.00
final: Farinas, 4.12.00

FILING MEETING MINUTES

NDA 20-771/S-004 – Action Package (second cycle)

Drug Product:	Detrol (tolterodine tartrate) Tablets
Sponsor:	Pharmacia & Upjohn Company
Indication:	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
Goal Date:	April 27, 2001
Review Team:	Brenda Gierhart, M.D. – Clinical Alexander Jordan, Ph.D. – Toxicology D. J. Chatterjee, Ph.D. – Biopharmaceutics David Lin, Ph.D. – Chemistry Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager
Division:	Division of Reproductive and Urologic Drug Products (HFD-580) Susan Allen, M.D., M.P.H. Director
Reviewer:	Evelyn R. Farinas, R.Ph., M.G.A. Regulatory Health Project Manager
Through:	Jeanine Best for Terri Rumble Acting Chief, Project Management Staff
Date:	April 3, 2001

On October 23, 2000, the Division issued an Approvable letter to the sponsor for Supplement 004. The letter stated that approval was dependent upon two conditions: the sponsor's submission of a draft label in accordance with the label enclosed in the October 23, 2000, letter; and satisfactory completion of the Division of Scientific Investigations' inspection of all study sites.

The sponsor's letter of October 26, 2000 constituted a complete response to our October 23, 2000, Approvable letter. The draft label submitted via facsimile to the sponsor on March 20, 2001, was accepted by Pharmacia & Upjohn, and is enclosed with the Approval letter that completes the review of this application. Please note that the Division of Scientific Investigations issued a final report on November 3, 2000, stating that the data submitted in support of this NDA by the three sites inspected (Drs. Antoci, Mitcheson, and Freedman) are acceptable.

In addition to the labeling recommendations for S-004, this package also includes labeling recommendations for Supplement [redacted]. These changes includ [redacted] in [redacted] and revisions to th [redacted]. An Acknowledge and Retain letter indicating that the approved label for Supplement 004 supercedes Supplements [redacted] will be issued.

/s/

Evelyn Farinas
4/3/01 10:24:04 AM
CSO

cover letter for action package first cycle

Jeanine Best
4/3/01 12:18:58 PM
CSO
Signing for Terri Rumble, CPMS

NDA 20-771/S-004 – Action Package (first cycle)

Drug Product:	Detrol (tolterodine tartrate) Tablets
Sponsor:	Pharmacia & Upjohn Company
Indication:	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.
Goal Date:	October 23, 2000
Review Team:	Brenda Gierhart, M.D. – Clinical Alexander Jordan, Ph.D. – Toxicology D. J. Chatterjee, Ph.D. – Biopharmaceutics David Lin, Ph.D. – Chemistry Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager
Division:	Division of Reproductive and Urologic Drug Products (HFD-580) Susan Allen, M.D., M.P.H. Director
Reviewer:	Evelyn R. Farinas, R.Ph., M.G.A. Regulatory Health Project Manager
Through:	Jeanine Best for Terri Rumble Acting Chief, Project Management Staff
Reviewer:	Evelyn R. Farinas, R.Ph., M.G.A. Regulatory Health Project Manager
Date:	October 23, 2000

Pharmacia & Upjohn submitted this SE-8 application (labeling application requiring review of clinical data) on December 23, 1999, to update the product labeling for the Clinical Studies and Adverse Reactions sections. This application did not include preclinical nor CMC data, not did it include Phase 4 commitments. Please note that foreign labeling, tradename review and pediatric information are not required for this application.

This abbreviated Action Package includes Clinical, Statistical, Biopharmaceutics and Chemistry Reviews, labeling (sponsor's proposal and FDA revisions), correspondence between the sponsor and the Division, and minutes of meetings and teleconferences.

In addition to the labeling recommendations on S-004, this package also includes labeling recommendations from DRUDP for [redacted]. These changes include revisions to the [redacted]

Please note that the indication will be modified from "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or

urge incontinence" to "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urge urinary incontinence, urgency and frequency."

/s/

Susan Allen
4/6/01 02:00:40 PM

Pharmacia & Upjohn

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

March 15, 2001

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 20-771/S-004
Detrol [tm]
Tolterodine tartrate tablets

Amendment #6

Dear Sir/Madam:

Reference is made to the package insert proposal faxed to Pharmacia Corporation on March 9, 2001. We have accepted the Division's proposals and have enclosed a final version of the package insert incorporating the proposed text. We are also sending an electronic version of the insert via secure
e-mail to farinase@cder.fda.gov.

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
Regulatory Affairs

GGS:kmv

Attachments

50 page(s) of revised draft labeling has been redacted from this portion of the review.

ORIGINAL

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

February 27, 2001

NDA SUPP AMEND

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

AJ 3/15/01
NAM

SE8 004 (BL)

Re: NDA 20-771/S-004
DETROL™
tolterodine tartrate tablets

Amendment #5 to Supplement

Dear Sir or Madam:

Reference is made to the Division's draft label faxed on February 15, 2001 concerning the above supplement. We have reviewed the Division's proposal and have provided our response in this submission. Enclosed please find a Marked Version, and a Clean Version of the PI.

In addition to the Marked Version and Clean Version of the PI, please find included in this submission the following attachments:

Attachment 1: Study 98-TOCR-007. Table 10, Mean Number of Incontinence Episodes/Week - ITT Population

Attachment 2: Pooled Adverse Event Table for Studies 94-OATA-008, -009, -010, 015, and 98-TOCR-007.

Attachment 3: Brown JH, Taylor P. Muscarinic receptor agonists and antagonists. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th edition. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. New York: McGraw-Hill 1996:148-154.

Attachment 4: Peters NL. Snipping the thread of life: Antimuscarinic side effects of medications in the elderly. Arch Intern Med 1989;149:2414-2430.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:lmf

Attachments

hold
NFI.
JTC
3/15/01

(3/6/01)
Reviewed;
See Memo
for comments
(label)
for sponsor

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

14 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-771/S-004

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

Dear Mr. Shawaryn:

We acknowledge receipt on October 27, 2000 of your October 26, 2000 resubmission to your supplemental new drug application for Detrol (tolterodine tartrate) tablets.

This resubmission contains additional revisions to the proposed label and the requested DSI information submitted in response to our October 23, 2000 action letter.

With this amendment, we have received a complete response to our October 23, 2000 action letter.

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

Sincerely,

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

/s/

Terri F. Rumble
11/2/00 02:48:09 PM

Pharmacia & Upjohn

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

October 26, 2000

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

NDA SUPP AMEND

ORIGINAL

SE8-004-AL

Re: NDA 20-771/S-004
DETROL™
tolterodine tartrate tablets

Amendment #4 to Supplement

Dear Sir or Madam:

Reference is made to the approvable letter dated October 23, 2000 concerning the above supplement.

This amendment addresses the comments included in this letter as follows:

1. We have reviewed the labeling included with the approvable letter (faxed to Pharmacia on October 4, 2000) and have proposed an alternate text to the Division's proposal. A strikethough/underlined version as well as a clean version of the package insert are provided in Attachment 1. Support for our proposals is appended to the strikethough/underlined version. Electronic copies, in Word, of both versions of the package insert are also included in this submission.

2. We have recently (October 17, 2000) received a request for additional information from DSI. This information was provided to DSI on October 25, 2000. It is our understanding that there are no outstanding issues with regard to site inspections.

3. There is no new safety information that has been collected directly pertinent to this supplement. The tolterodine tablets portion of the protocol (98-TOCR-007) that was the basis of this supplement was complete at the time of the original submission. Other safety data relative to this compound is routinely reported through periodic safety updates and

annual reports to NDA 20-771 and through information amendments and annual reports to IND 46,169. Since this submission, a Periodic Safety Update Report has been submitted to NDA 20-771on July 5, 2000, an annual report to NDA 20-771 has been submitted on May 12, 2000. The annual report to IND 46,169 is in preparation and should be submitted to the Division in the next week.

We consider this amendment to be a complete response to the October 23, 2000 approvable letter.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

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

GGS:lmf

Attachment

AP letter to be issued in April '01 based on Labeling faxed by sponsor on 3/20 GGS

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

3-22-01
CSO INITIALS DATE

15 page(s) of revised draft labeling has been redacted from this portion of the review.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 3, 2000

TO: Mr. Gregory G. Shawaryn, Regulatory Manager,
Regulatory Affairs, Pharmacia & Upjohn

FROM: Dornette Spell-LeSane, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: NDA 20-771, Pharmacia & Upjohn Company, Detrol™

The following are additional Clinical Pharmacology and Biopharmaceutical labeling comments and request for information related to the review of your NDA 20-771 for Detrol™.

1. Please provide a rationale for addressing the issue of risk (if any) associated with the exceptionally high levels of metabolites in renally impaired patients.

2. A recommendation for dosage adjustment (for renally impaired patients) in the final label will be provided.

If you have any questions please call me at 301-827-4260,

Sincerely

/S/

Dornette Spell-LeSane

cc:
Archival IND/NDA 20-771
HFD-580/Div. Files
HFD-580/Allen/Shames/Geirhart/Parekh/Chaterjee

Drafted by: Spell-LeSane, 10.3.00
Initialed by: Chatterjee, 10.3.00
Final: Spell-LeSane, 10.3.00
Filename: memo.doc

MEMORANDUM

Gierhart

SEP 29 2000

NDA 20-771, —, S-004, —

INFORMATION REQUEST LETTER

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

Dear Mr. Shawaryn:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol (tolterodine tartrate) tablets.

We also refer to your submissions dated January 12, March 14, and December 22, 1999, and June 9, 2000.

We are reviewing your proposed Physician Package Insert for this application. Note that there will be additional comments to the Clinical Pharmacology section sent to you at a later date.

Please review the attached document and provide your prompt written response to continue our evaluation of your supplemental application.

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

Sincerely,

/S/ 9/28/00

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

Attachment

cc:
Archival NDA 20-771
HFD-580/Div. Files
HFD-580/E.Farinas
HFD-580/Allen/Shames/Hirsch/Gierhart/Parekh/Chatterjee/Rhee/Lin/Jordan

DISTRICT OFFICE

Drafted by: erf/September 27, 2000
Initialed by: rumble/
final:erf
filename: N20771.DOC

INFORMATION REQUEST (IR

15 page(s) of revised draft labeling has been redacted from this portion of the review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Gerhart

Food and Drug Administration
Rockville MD 20857

SEP 1 3 2000

David Mitcheson, M.D.
Bay State Urologists, Inc.
11 Nevins Street
Brighton, Massachusetts 02135

Dear Dr. Mitcheson:

Between May 23 and June 1, 2000, Mr. Gary Hagan, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #98-TOCR-007) of the investigational drug, Detrol® (tolterodine tartrate) tablets, performed for Pharmacia & Upjohn Company. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hagan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research,
7520 Standish Place
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm. NDA 20-771/S-004
HFD-580/Farinas
HFD-580/Hirsch
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File #010136
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-NE252/Kraychuk
HFR-NE250/Levitt
HFR-NE250/Hagan

CFN #

Field Classification: NAI

Headquarters Classification:

__X__1)NAI
_____2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-WL warning letter
_____6)OAI-NIDPOE

Note to the File:
This inspection covers both NDA 20-771/S-004 and NDA 21-228. The difference is that the latter provides for an extended release formulation of the drug.

E:/blay/mitcheson.rab
drafted/rab/8.30.00
reviewed:/
final:mgk 9/6/00

Note to Review Division and DSI Recommendation:

The field inspector reviewed the study–related records for 7 of the 37 patients enrolled in protocol #98-TOCR-007 at Dr. Mitcheson's site. The inspector reviewed an additional 6 records of the 30 subjects who continued into the open-label portion of the study. The data appear acceptable for use in support of drug claims.

ORIGINAL

Pharmacia & Upjohn

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

August 28, 2000

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

SUPPL NEW CORRESP

S-004

Re: NDA 20-771/S-004
DETROL™
tolterodine tartrate tablets

Amendment #3 to Supplement

Dear Sir or Madam:

Pharmacia and Upjohn has recently submitted IND amendment Serial No. 40 to IND 56, 406 which contained amendment 4 to protocol 98-TOCR-007. Since this protocol was a significant component of the above submission, we provide a copy of this IND amendment to the above file for completeness.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

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

GGS:mlw

Attachment

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☒ N.A.I. ☐ MEMO
GGS 8-31-00
CSO INITIALS DATE

Pharmacia & Upjohn

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

August 21, 2000

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

Serial No. 040

Re: IND 56,406
Tolterodine Prolonged Release Capsules
for treatment of overactive bladder

Protocol Amendment
Change in Protocol

Sir/Madam:

We are amending the above referenced IND to provide information as described below:

Item 6-Protocols

Change in Protocol

Protocol 98-TOCR-007, Clinical efficacy and tolerability/safety of tolterodine prolonged release capsules and tolterodine immediate release tablets vs placebo. A randomized, double-blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder. *(Protocol and Amendment 1 submitted in Serial No. 008, dated 1/20/99, amendments 2 and 3 submitted in Serial No. 016, dated 5/21/99).*

Protocol Amendment 4 issued on July 2, 1999 is attached. It provides for the addition of clinical sites and an update of the statistical and analytical plans.

It is Pharmacia and Upjohn's standard procedure to submit changes to protocols in a timely manner, unfortunately, due to an administrative oversight, submission of this amendment was inadvertently omitted. We have just recently learned of this omission and are now submitting the amendment to the IND. A copy of this submission is being submitted to NDA 20-771 (S-004) and NDA 21-228. Protocol 98-TOCR-007 is a significant part of these submissions.

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

cc Desk copy to Evelyn Farinas HFD-580, Room 17B-45

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 16, 2000

To: Gregory G. Shawaryn, Regulatory Manager, Regulatory Affairs
Pharmacia & Upjohn Company

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

Subject: NDA 20-771, S-004, Detrol (tolterodine tartrate) tablets

The sponsor was asked (via telephone conversation between Ms. Farinas and Mr. Shawaryn) to submit a copy of Amendment 4 to Protocol 98-TOCR-007. This submission arrived on August 29, 2000. Upon review, the sponsor was requested via regulatory IR letter to IND 56,406 dated September 12, 2000, to provide the following clarifications:

1. Define what was meant by the term "estimations" in this protocol (i.e. Protocol Amendment #4, 10 Statistics, 1. Intention-to-treat population).

2. Describe how the estimations were performed.

3. Provide the list of subjects who had their micturition chart diary data estimated.

Evelyn R. Farinas
Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Hirtle Gerhart
DOC Rm.

Food and Drug Administration
Rockville MD 20857

AUG 8 2000

Joseph P. Antoci, M.D.
Connecticut Clinical Research Center
160 Robbins Road
Waterbury, Connecticut 06708

Dear Dr. Antoci:

Between July 10 and July 18, 2000, Ms. M. Patricia Murphy, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #98-TOCR-007) of the investigational drug, Detrol® (tolterodine tartrate) tablets, performed for Pharmacia & Upjohn Company. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Murphy during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John K. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm. NDA 20-771/S-004
HFD-580/Farinas
HFD-580/Hirsch
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File #010152
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-NE252/Kraychuk
HFR-NE250/Levitt
HFR-NE2530/Murphy

CFN #

Field Classification: NAI

Headquarters Classification:

_X_ 1)NAI
_____ 2)VAI no response required
_____ 3)VAI-R response requested
_____ 4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____ 5)OAI-WL warning letter
_____ 6)OAI-NIDPOE

E:/blay/antoci.rab
drafted/rab/8.4.00
reviewed:/
Final:mgk 8/7/00

Note to Review Division and DSI Recommendation:

The field inspector reviewed the study–related records for 21 of the 38 patients enrolled in protocol #98-TOCR-007 at Dr. Antoci's site. The data appear acceptable for use in support of drug claims.

Pharmacia & Upjohn

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

July 14, 2000

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 20-771/S-004
DETROL™
tolterodine tartrate tablets

NDA SUPP AMEND
SE8-004-

Amendment #2 to S-004

Dear Sir or Madam:

In response to Evelyn Farinas's June 28 request, please find the following attachments relative to evaluation of adverse events relative to certain subgroups pooled across protocols 94-OATA-008, 94-OATA-009, 94-OATA-010, 94-AOTA-015 and 98-TOCR-007.

Attachment 1: Events sorted relative to poor or extensive metabolizers
Attachment 2: Events sorted by age
Attachment 3: Events sorted by race
Attachment 4: Events sorted by sex

Based upon Pharmacia & Upjohn's review of these data, there does not appear to be a difference in safety profile of tolterodine base on metabolism, age, race or sex.

If you have any questions regarding this submission, please contact Gregory Shawaryn at (616) 833-8239. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:LMF
Enclosure

(9/13/00) Reviewed in MO Review of SE8-004 NAI BSG

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Pharmacia & Upjohn

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

May 5, 2000

ORIGINAL

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

NDA SUPP AMEND

Re: NDA 20-771/S-004
DETROL™
tolterodine tartrate tablets

Amendment No. 1 to S-004

Dear Sir or Madam:

SE8-004-BM

In response to Evelyn Farinas's April 27 request, please find in Attachment 1 the Observed Cases analysis described in protocol 98-TOCR-007. This analysis was not included in the study report for reasons described in the Attachment.

If you have any questions regarding this submission, please contact Gregory Shawaryn at (616) 833-8239. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:lmf

Enclosure

(9/13/00)
Reviewed in MO Review of SE8-004;
NAI
BSC

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmacia&Upjohn

ORIGINAL

Global Intellectual Property

May 1, 2000

NEW CORRESP

NC

Via Airborne Express
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Rm. 2-14
12420 Parklawn Drive
Rockville, MD 20857

Re: NDA 020771
DETROL (tolterodine tartrate)

Time Sensitive Patent Information

To Whom It May Concern:

Enclosed please find duplicate originals of patent information for the above-referenced product.

Very truly yours,

Bruce A. Pokras

Bruce A. Pokras

Enclosures

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmacia & Upjohn
100 Route 206 North
Peapack, NJ 07977

Bruce A. Pokras
Senior Patent Counsel
Voice: (908) 306-8453
Fax: (908) 306-8650
bruce.a.pokras@am.pnu.com

Farinas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-771/S-004

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001

DEC 29 1999

Attention: Gregory G. Shawaryn,
Regulatory Affairs

Dear Mr. Shawaryn

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Detrol™ (tolterodine tartrate) Tablets

NDA Number: 20-771

Supplement Number: S-004

Date of Supplement: December 22, 1999

Date of Receipt: December 23, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on Febeurary 21, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

19

Terri F. Rumble
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:
Original NDA 20-771/S-004
HFD-580/Div. Files
HFD-580/CSO/E. Farinas

SUPPLEMENT ACKNOWLEDGEMENT

NDA NO. 20-771 REF. NO. SE8-004
NDA SUPPL FOR Labeling

Pharmacia & Upjohn

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

December 22, 1999

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 20-771
DETROL™
tolterodine tartrate tablets

Efficacy Supplement

Dear Sir/Madam:

Under the provisions of 21 CFR 314.70, Pharmacia & Upjohn is submitting this Supplement to the above referenced NDA.

As part of the development program for the prolonged release formulation of tolterodine (subject of IND 56,406), a large placebo–controlled double blind study (study 007) was conducted to compare the effects of tolterodine immediate release (Detrol), tolterodine prolonged release, and placebo on the primary efficacy variable of urinary incontinence. More than 500 patients were treated in each arm of this study. The study report is now complete and results indicate a highly statistically significant difference between Detrol and placebo for improvement in incontinence episodes with Detrol. Treatment with Detrol also resulted in statistically significant improvement in secondary efficacy variables, number of micturitions and mean volume voided. Adverse event frequencies were similar to those reported as part of the original NDA 20-771. As such we have prepared this supplemental application to update the product labeling (Clinical Studies and Adverse Reactions sections) to reflect these new findings and additional experience in this study, which enrolled more patients than the combined total for the 3 registration studies included in the original NDA.

This application contains:

Items 1, 2, 8, 10, 11, 12, 16, 18, and 19.

Items 1, 2 (paper and electronic), 11 (electronic only), 12 (electronic only), 16, 18 and 19 are included in volume 1. Items 8/10 (final report for study 007) are included in volumes 2 through 23. An electronic copy of this study report is also included.

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, September 1997. The total size of the electronic files on CD-Rom is 394 megabytes, Item 11, 51 megabytes and Item 12, 343 megabytes. These files have been scanned with Network Associates' McAfee Virus Scan software for Windows, version 4.01. All electronic information is contained in the directory N20771 and a copy of this letter and the 356H form are also provided as a 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 N20771. 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.

A User Fee check made payable to the Food and Drug Administration in the amount of $144, 878 was sent to the Mellon Bank, Pittsburgh, PA. on December 17, 1999.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:lmf

Attachments

cc: Nancy Ostrove DDMAC

regfiles

From: regfiles [regfiles@gateway.pnu.com]
Sent: Tuesday, March 20, 2001 10:17 AM
To: Evelyn Farinas 301-827-4260 FAX 301-443-9288
Subject: DETROL PI T-Con with FDA

ArchiveCopy: regfiles@gateway.pnu.com
Product Name: DETROL
Product Number: NDA 20-771

PNU320PI.DOC

Dear Evelyn,

Per the telephone contact March 20, 2001, between Pharmacia and FDA, we agree with all requested revisions discussed regarding the DETROL Tablets package insert (PI). Supplements [redacted] -004, [redacted] have been considered, with changes to the PI incorporated. The attached WORD version of the Detrol Tablets PI reflect the changes discussed today (with the exception of the decimal alignment in Tables 2 and 3 -- these will be decimal aligned in the 'printed' PI as discussed).

Thank you and best regards,

Dora

Attachment

PHARMACIA & UPJOHN, INC. FACSIMILE

7000 Portage Road
Kalamazoo, MI 49001
Facsimile #: 616-833-8237

TO: Evelyn Farinas

DATE: September 21, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA 20-771 S-004

FROM: Gregory Shawaryn
PHONE: 616-833-8239

TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 1

Message:

Dear Evelyn,

On September 15 you asked me to check if the following statement is accurate:

"

To make the statement accurate it would need to be revised in either of the following ways:

OR

2. "Phase 2 and 3 clinical trial program for Detrol tablets included 3071 patients who were treated with Detrol (n=2133) or Placebo (n=938). The patients were treated with 1,2,4 or 8 mg/day for up to 12 months"

The 2133 figure included 70 patients on 0.5mg Detrol BID and 58 patients treated with 4 mg BID as well as 2005 patients on 2 or 4 mg/day.

Please give me a call at 616-329-8239 if you have any questions or concerns.

Sincerely,
Gregory Shawaryn

Freedman

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 3, 2000

TO: Evelyn Farinas., Regulatory Project Manager, HFD-580
Dan Shames, M.D. Medical Officer, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.,
Senior Regulatory Review Officer
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-771/S-004 and 21-228

APPLICANT: Pharmacia & Upjohn

DRUG: Detrol® (tolterodine tartrate) tablets

THERAPEUTIC CLASSIFICATION: 1(S)

INDICATION: Treatment of overactive bladder

REVIEW DIVISION GOAL DATE: September 22, 2000
ACTION GOAL DATE (PDUFA Date): October 22, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this drug is the treatment of overactive bladder.

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
David Mitcheson, M.D.	Brighton, MA	3 May 2000	12 July 2000	NAI/010136
Joseph Antoci, M.D.	Waterbury, CT	3 May 2000	3 Aug 2000	NAI/010152
Sheldon Freedman, M.D.	Las Vegas, NV	3 May 2000	2 Oct 2000	VAI-R/010202

Site #1
David Mitcheson, M.D.
Bay State Urologists, Inc.
11 Nevins Street
Brighton, Massachusetts 02135
Acceptable

a. The field investigator inspected the study-related records for 7 of the 37 subjects enrolled at Dr. Mitcheson's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable. No Form 483 was issued.

Site #2
Joseph P. Antoci, M.D.
Connecticut Clinical Research Center
160 Robbins Road
Waterbury, Connecticut 06708
Acceptable

a. The field inspector inspected the study-related records for 21 of the 38 subjects entered into the study at Dr. Antoci's site.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable. No Form 483 was issued.

Site #3
Sheldon Freedman, M.D.
3006 S. Maryland Parkway
Las Vegas, Nevada 89109
Acceptable

a. The field investigator inspected the study-related records for 8 of the 40 subjects enrolled at Dr. Freedman's site.

b. There were no limitations on the inspection.

c. A Form 483 was issued for several instances of failure to follow protocol and maintain adequate and accurate records, as well as failure to retain an informed consent form for one patient. These deficiencies are of relatively minor importance. Original subject diaries were requested from the sponsor. These diaries were reviewed to substantiate the observations made by the inspector (who conducted the inspection using photocopies of the original diaries). An additional four diaries were reviewed in their entirety and compared against the database submitted in the NDA. No additional discrepancies were observed. Because of the nature and number of violations observed, a VAI-R letter was sent to Dr. Freedman requesting assurances that these violations would not occur in ongoing or future studies.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Drs. Antoci, Mitcheson, and Freedman are acceptable.

Follow-up action: None needed.

/S/

Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations

DISTRIBUTION:

NDA 20-771 and 21-228
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-580/Farinas
HFD-46/Blay
HFD-46/Huff
HFD-46/CIB File #s 010136, 010152, and 010202
HFD-46/Reading File

MEMO: Sites for FDA Inspections (NDA 20-771 SE8-004 and NDA 21-228 both Detrol)

To: **Evelyn Farinas, Project Manager, HFD-580 and Roy Blay, Ph. D., DSI**

From: **Brenda Gierhart. Medical Officer, HFD-580**

19
3/10/00

Date: **3/10/00**

I recommend that the following three sites be inspected. They are the sites with the largest enrollments. There was the same one large randomized comparitive placebo-controlled clinical trial in NDA 20-771 SE8-004 and NDA 21-228. The trial had three arms: Detrol immediate release, Detrol extended release, and placebo.

Protocol 98-TOCR-007

1)	**Site #203-Joseph Antoci, MD** **Medical Practice** **160 Robbins Street** **Waterbury, CT 06708 USA**	**34 Enrolled Subjects**
2)	**Site #219-Sheldon Freedman, MD** **3006 South Maryland Parkway, #430** **Las Vegas, NV 98109, USA**	**40 Enrolled Subjects**
3)	**Site #239-David Mitcheson, MD** **Bay State Urologist Inc** **11 Nevin Street, Suite 501** **Brighton, MA 02135 USA**	**37 Enrolled Subjects**

cc Original NDA 20,771
Original NDA 21,228
B. Gierhart. MD HFD-580
E. Farinas, PM HFD-580
R. Blay, PhD DSI

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Clinical Pharmacology and Toxicology Review
Action:	Not applicable for this application
Date:	April 3, 2001

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate)tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Advisory Committee
Action:	Not applicable for this application
Date:	April 3, 2001

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate)tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Advisory Committee
Action:	Not applicable for this application
Date:	October 23, 2000

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Foreign Labeling
Action:	Not applicable for this application
Date:	October 23, 2000

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Tradename Review
Action:	Not applicable for this application
Date:	April 3, 2001

NDA 20-771/S-004

Drug Name:	Detrol (tolterodine tartrate) tablets, 1 and 2 mg
Sponsor:	Pharmacia & Upjohn
Subject:	Tradename Review
Action:	Not applicable for this application
Date:	October 23, 2000