CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

DDMAC review

DDMAC's comments were incorporated in the Medical Officer's Review.

Number of Pages Redacted 17

❖❖❖

Draft Labeling
(not releasable,

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

DATE RECEIVED: 11/ 21/ 2000	DUE DATE: 12/ 15/ 2000	OPDRA CONSULT #: 00-0312

TO:

Susan Allen
Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

THROUGH:

Evelyn Farinas
Project Manager
(HFD-580)

PRODUCT NAME [redacted] (tolterodine extended-release capsules)

NDA #: 21-228

MANUFACTURER: Pharmacia &Upjohn

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:

OPDRA does not recommend the use of the proposed proprietary name, [redacted]', for tolterodine extended-release capsules. See review for details.

/S/ 12/14/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 12/18/00

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE REVIEWED: December 1, 2000

NDA#: 21-228

NAME OF DRUG: [redacted] (tolterodine extended-release capsules)

NDA HOLDER: Pharmacia & Upjohn

I. INTRODUCTION:

This consult is in response to a November 21, 2000 request, by the Division of Reproductive and Urologic Drug Products, to review the proposed proprietary drug name, [redacted] regarding potential name confusion with other proprietary/generic drug names.

[redacted] is a *third* proposed proprietary name for this product. OPDRA previously reviewed the name, Detrol and Detrol LA, on October 2, 2000, and had *no objections* to the use of the name, Detrol LA. However, [redacted] was not recommended due to the possible name confusion with Ditropan XL. The sponsor requested that [redacted] be considered the new primary choice for the proprietary name.

PRODUCT INFORMATION

[redacted] (tolterodine extended-release capsules) is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. It is indicated for the treatment of [redacted] The recommended dose is 4 mg once daily. The dose may be lowered to 2 mg daily based on individual response and tolerability. [redacted] capsules are supplied as 2 mg and 4 mg strengths.

II. RISK ASSESSMENT:

A. EXPERT PANEL DISCUSSION

An expert panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, [redacted] Potential concerns regarding drug marketing and promotion related to these proposed names were also discussed. This group is composed of OPDRA medication errors prevention staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

According to the panel, the proposed name, [redacted] is still too close to Ditropan XL. The modifiers for these two drugs could look-alike on handwritten prescriptions. DDMAC had no objections to the proposed proprietary name in regard to promotional claims.

B. SAFETY EVALUATOR RISK ASSESSMENT

Although the modifier, XR, has been used in proprietary names of extended-release formulations such *as Tegretol-XR, Voltaren XR, Dilacor XR, Diltiazem XR, Glucophage XR,* and *Effexor XR*, the safety concern is at "XR" is not distinctively different from "XL" when scripted, and therefore, the handwritten prescriptions of ——— ." could look-alike "Ditropan XL."

In order to determine if the modifiers, "XL," and "XR," have been confused for one another, a search in the *Adverse Event Reporting System (AERS)* was performed for any post-marketing safety reports of medication errors associated with these modifiers. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, *"Tegretol XR%, Voltaren XR%, Dilacor XR%, Diltiazem XR%, Glucophage XR%, Effexor XR%, Biaxin XL%, Lodine XL%, Lescol XL%, Glucotrol XL%, Toprol XL%, Procardia XL%, Ditropan XL%, and Minipress XL%,"* were used to perform the searches.

The search results revealed a medication error report involving the modifiers, "XL" and "XT." According to a report (ISR#: 3271042-7), a prescription for Toprol XL 100 mg was dispensed as Tegretol XR 100 mg on May 11, 1999. The patient discovered the error and returned to the pharmacy. According to the reporter, the various modifiers such as XL and XR can cause confusion and errors could occur.

The above example confirms the potential for confusion between the modifiers, "XR" and "XL," on prescriptions when combined with similar proprietary names. Given the fact that Detrol has already been confused with Ditropan XL (see OPDRA consult# 00-190), the proposed name, ' ——— objectionable at this time.

III. RECOMMENDATION:

?DRA does not recommend the use of the proposed proprietary name, ' ——— ', for tolterodine extended-release capsules

If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3161.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 12/14/2000

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

CC:

NDA: 21-228
Office Files
HFD-580; DivFiles; Evelyn Farinas, Project Manager
HFD-580; Susan Allen, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002: Heidi Jolson, Acting Deputy Center Director for Review Management
HFD-400: Peter Honig, Director, OPDRA
HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-400: Sammie Beam, Project Manager, OPDRA

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

Pharmacia & Upjohn

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

November 15, 2000

over LA

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

NEW CORRESP

NIC

RE: NDA 21-228
Tolterodine extended release capsules

General Correspondence
Expedited Review/Comment Requested

Dear Sir/Madam:

Reference is made to November 9, 2000 telephone contact with Evelyn Farinas and Dr. Gierhart regarding Pharmacia & Upjohn's (P&U) trademark proposal for the above product. In that conversation P&U was informed that there was unanimous agreement within the Division to support the OPDRA recommendation that due to potential confusion with another product, the — suffix was not acceptable. The "LA" suffix was approved. FDA also confirmed in this contact that the established name for the product would be "extended" release capsules rather than — release capsules as originally submitted.

Since use of — has been rejected, we request that the FDA consider ' — as a new primary choice for the suffix for the extended release product "

Although we believe "LA" for "long acting" is a useful and descriptive suffix, and a good backup, the suffix " — ' clearly denotes the "Extended Release" formulation, is a more contemporary designation, and better communicates to patients and physicians the properties of the formulation. The agency as recently as October 2000, has approved "XR" to denote the extended release formulation of Glucophage. Hopefully, the research conducted relative to this product will be useful in evaluation of] ' and expedite the process.

It is our intent to work constructively with the Division towards an approval action for this NDA on or before the primary action date of December 28, 2000.

If you should have any question 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: Jerry Phillips, OPDRA-HFD 400

APPEARS THIS WAY
ON ORIGINAL

To Teri 11/21

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Associate Director, Medication Error Prevention
e of Post Marketing Drug Risk Assessment, HFD-400
15B-03, PKI N Bldg.)

FROM: Evelyn R. Farinas, R. Ph., M.G.A.
Project Manager, DRUD, HFD-580
301-827-4271

DATE	IND NO.	NDA NO. 21-228	TYPE OF DOCUMENT sponsor's letter requesting [redacted] e for consideration	DATE OF DOCUMENT November 15, 2000
November 21, 2000				

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG GU	DESIRED COMPLETION DATE
Tolterodine extended release	urgent		December 15, 2000

NAME OF FIRM: Pharmacia and Upjohn

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES TOCOL REVIEW ER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Please note that this is the third name that sponsor is proposing. Dr. Lee from OPDRA already finished and sent to the DRUDP a consult with the two original names proposed by the sponsor. The Division agreed with OPDRA that for safety considerations Detrol LA [redacted], and so notified the sponsor on the week of November 6, 2000, via teleconference. Let me know if you need any additional background materials, or if I could be of help.
Thanks,

PDUFA DATE: December 2[redacted]2000
ATTACHMENTS sponsor's letter
Archival IND/NDA [redacted]
HFD-[redacted]/Division File
F [redacted]/RPM
[redacted]/Reviewers and Team Leaders

SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one)	
/S/ 11/21/00		☒ MAIL	☐ HAND
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER	

DEPARTMENT OF HEALTH AND HU[redacted]
PUBLIC HEALTH SERV
FOOD AND DRUG ADMINISTRATION

[redacted] R CONSULTATION

TO (Division/Office)			FROM:	
OPDRA			Evelyn R Farinas, Project Manager HFD 580	
J 3/95	IND NO. 50046	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT Oct 15/96
NAME OF DRUG Tolterodine 56406		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Antimuscarinic Agent	DESIRED COMPLETION DATE Dec 1/96

NAME OF FIRM
Pharmacia & Upjohn

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ SOLUTION
- ☐ AVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please review and comment attached proposal to incorporate imprint on capsule. Please provide rationale/comments on other products which already have images or shapes on tablets/capsules.

Thanks!

Please comment on appropriate Regulations that apply – i.e. are there Regs that apply to imprints

Please see 206.10 on Code Imprint Regs – : Code imprint means any single letter or number or any combination of letters + numbers, including eg w. its company name, + NDC or a mark, symbol, logo, or monogram or combination of letters + is sometimes acceptable.

/S/

METHOD OF DELIVE ☒ MAIL ☐ HAND

SIGNATURE OF RECEIVER /S/ 11/3/96

SIGNATURE OF DELIVERER /S/

FORM FDA 3291 (7/83)

U.S. GPO 1990-698-701/40017

D11

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

OCT 2 2000

DATE RECEIVED: 7/ 18/ 2000	DUE DATE: 9/ 22/ 2000	OPDRA CONSULT #: 00-0190

TO:
Susan Allen
Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

THROUGH:
Evelyn Farinas
Project Manager
(HFD-580)

PRODUCT NAME: ——— (tolterodine ——— -release capsules) NDA #: 21-228	MANUFACTURER: Pharmacia &Upjohn

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of the modifier, ——— for tolterodine extended-release capsules. However, the use of the alternate modifier, "LA", is not objectionable.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 9/28/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ '00

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE REVIEWED: September 12, 2000

NDA#: 21-228

NAME OF DRUG: ——— tolterodine ——— -release capsules)

NDA HOLDER: Pharmacia & Upjohn

I. INTRODUCTION:

This consult is in response to a July 18, 2000 request, by the Division of Reproductive and Uroiogic Drug Products, to review the proposed proprietary drug name ——— , and the alternate name, Detrol LA, regarding potential name confusion with other proprietary/generic drug names. Container labels, carton labeling, and the package insert were also submitted for review of possible interventions in minimizing medication errors.

etrol (NDA 20-771) tablets were approved on Mar 25, 1998, and are available as 1 mg and 2 mg strengths.

PRODUCT INFORMATION
Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. It is indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, and/or urge incontinence. The recommended dose is 4 mg once daily. The dose may be lowered to 2 mg daily based on individual response and tolerability. Tolterodine capsules are supplied as 2 mg and 4 mg capsules.

II. RISK ASSESSMENT:

The standard OPDRA proprietary name studies were not conducted for this consult since the proprietary [illegible] since its approval in 1998. An E[illegible] discussion was conducted to address potential safety concerns regarding the modifier, ——— Moreover, since Detrol is an approved drug, a search in the Adverse Event Reporting System (AERS) and the Drug Quality Reporting System (DQRS) was conducted using the search terms, *Detrol%* and *tolterodine%* , for any medication error reports.

A. EXPERT PANEL DISCUSSION

An expert panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary ame, ——— and the alternate name, Detrol LA. Potential concerns regarding drug marketing and omotion related to these proposed names were also discussed. This group is composed of OPDRA medication errors prevention staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

According to the panel, the modifier, [redacted] is often used for extended-release products. However, [redacted] could be confused with "SL," which is an abbreviation for sublingual administration. DDMAC had no objections to the proposed proprietary name in regard to promotional claims.

AERS and DQRS Searches

OPDRA conducted a search for post-marketing medication error reports associated with the proprietary name Detrol, using the Meddra term, "Drug Maladministration. This search was conducted to determine if there is any current confusion with the use of the name, Detrol.

The search revealed five (5) medication error reports of name confusion between Detrol and other proprietary names. Results are listed in Table I. *(See Appendix A for full text narratives of the medication error reports.)*

In addition, there were three (3) medication error reports regarding the safety concerns of approving the proprietary name [redacted]. Results are summarized in Table II. *(See Appendix B for full text narratives of the medication error reports.)*

Table I (Name confusion between Detrol and another drug name)

	Intended	Dispensed	Outcome	Cause	AERS/DQRS #
1	Detrol 2 mg	Prandin 2 mg	Not administered	Order entry error	3539673-4
2	DDAVP	Detrol 2 mg	Headache, urine with strong odor	Dispensing error	3392211-1
3	DDAVP	Detrol	Urinary retention, trouble sleeping	Dispensing error	3309265-0
4	Septra	Oxybutynin	Muscle spasm	Verbal miscommunication	3408593-8
5	Prenatal vitamins	Detrol	Death	Dispensing error	3297963-7

Table II (Safety concerns regarding [redacted])

	Safety Concern	Recommendation	AERS/DQRS #	Reporter
1	[redacted]		3484866-8	Physician, Director of Evanston Continence Center at Norwestern University Medical School & Secretary-Treasurer of International Urogynecological Association
2	[redacted]		3484938-8	Physician, Medical Director of Urology Institute Center for Bladder Disorders at Methodist Hospital & Associate Professor at Baylor College of Medicine
3	[redacted]		3484937-6	Physician, Head of Voiding Dysfunction, Department of Urology, Cleveland Clinic Foundation

In the first set of these medication error reports, Detrol was confused with *Prandin, DDAVP, Septra*, and an unspecified *prenatal vitamins*. Prandin, which is also available as a 2 mg strength, was entered incorrectly into the computer by a technician and dispensed to the patient without a final check by the pharmacist. DDAVP, which has the same numerical strength (0.1 mg, 0.2 mg) as Detrol (1 mg, 2 mg), was inadvertently dispensed with Detrol, but the exact causes of these errors were not specified. Moreover, oxybutynin was dispensed instead of Septra because a prescription was written for both Septra and oxybutynin on the same prescription pad, and the patient instructed the pharmacist to fill one of the drugs that was listed on the prescription. Since the patient was already taking Detrol at home, the patient instructed the pharmacist to fill Septra. However, the patient pointed to oxybutynin on the prescription, and the pharmacist filled this drug. The patient did not recognize the difference between oxybutynin and Detrol. In addition, a medication error involving Detrol and prenatal vitamins lead to the death of a fetus, but the nature of the dispensing error or the specific name of the drug were not available. In these five reports, the problem concerning name confusion is not easily addressed

since these reports did not reveal apparent causes or consistent pattern of errors. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Detrol. However, based on these reports, OPDRA has no recommendations at this time.

In regard to the medication error reports involving [redacted], three (3) reporters addressed safety concerns of name confusion with Ditropan XL. One reporter's concern is that Ditropan XL (oxybutynin) is marketed to patients with overactive bladder and is the primary competition for Detrol (tolterodine). Although the dosages for these two medicines are quite different, the patients could confuse the two drugs and take the wrong medication because of similar names. In that case, some patients could have allergic reactions to oxybutynin or tolterodine. Moreover, many of the patients who use these drugs are elderly and are in institutionalized or assisted living communities. The reporter also specified that "even now, there are patients who confuse Detrol with Ditropan XL." Therefore, naming the once daily product as [redacted] would complicate this name confusion. The second reporter stated that the potential name confusion is obvious since Ditropan XL is the only once daily anticholinergic on the market for overactive bladder symptoms, and the medical field already has a real problem with similar names. This reporter stated that ' [redacted] ' would imply the same drug benefit without the name confusion. The third reporter stated that dispensing errors between Ditropan XL and [redacted] could cause significant problems with respect to the drug's hypersensitivities and pregnancy categories, where Ditropan has been classified in pregnancy category B, but Detrol has been classified in category C. Moreover, since both Ditropan XL (5, 10, 15 mg; titrated up to 30 mg) and [redacted] are titrated differently for each individual, there could be pharmacy confusion. This reporter suggested " [redacted] ' as modifiers for the proposed drug.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. The modifier, XL, is a known medical abbreviation for "extended-release" formulations. Examples include Biaxin XL, Ditropan XL, Glucotrol XL, Lodine XL, Minipress XL, Procardia XL, and Toprol XL. However, this modifier has been misinterpreted for "SL", which is an abbreviation for "*sublingual*" administration. In the case with Procardia XL, the liquid-filled nifedipine capsules were punctured and administered under the tongue because the modifier, "XL", was verbally misunderstood for sublingual *(SL)* off-labeled use. However, since the proposed drug is supplied as capsules composed of approximately 1mm diameter film-coated prolonged-release beads, the safety risk is minimal in this case.

2. According to the applicant, the established name of the proposed drug is tolterodine *prolonged-release* capsules. However, this modifier is not an official dosage form in the United States Pharmacopeia (USP) monographs. According to the USP 24 NF 19 [1151], "expressions such as "prolonged-action," "repeat-action," and "sustained-release" have been used" to describe dosage forms. However, "the term, "extended-release" is used for Pharmacopeial purposes." Moreover, according to the Division's chemist (HFD-580), *"the term, "extended-release" is most frequently used for modified release dosage forms that are not considered delayed-release. Since the proposed drug is not a delayed-release product, the preferred terminology is extended-release."*

3. There are safety concerns regarding the possible name confusion between [redacted] and Ditropan XL. As stated above, one reporter alluded to the fact that there are patients who confuse the approved drug, Detrol, with Ditropan XL due to their similar drug names despite the different strengths and doses. If [redacted] also becomes available, name confusion could escalate since the longer-acting [redacted] resembles Ditropan XL more closely than Detrol due to the use of the same modifier, "XL." Moreover, since both of these drugs are used for the treatment of overactive bladder with the symptoms of urinary frequency, urgency, and urge incontinence, these two drugs would be prescribed in the same population. Furthermore, both drugs are recommended for once-daily administration, and therefore, prescriptions for these two drugs could appear similar. Although we recognize that the different formulations and strengths would help differentiate between [redacted] and Ditropan XL, misadventures or substitution of

these two drugs could have significant outcomes for those patients who have hypersensitivities to either of the active components of these drugs. Moreover, as previously mentioned in the medication error reports, these two drugs are classified in different pregnancy categories. Although it is difficult to assess the magnitude of the name confusion between Detrol and Ditropan XL in current practice from the limited number of medication error reports, this review indicates that the addition of the same modifier, "XL" could potentially cause name confusion between the proposed product and Ditropan XL. Since there are other modifiers that can be used to indicate an extended-release formulation, the use of the term, "XL," is not recommended in this case.

4. In the process of reviewing the proposed drug name, we discovered sixteen (16) medication error reports of labeling confusion between Detrol 1 mg and 2 mg strengths. According to these reports, both Detrol 1 mg and 2 mg packages and tablets are almost identical. First, the printing on the unit-dose blister tablets is hard to read and very light except for the manufacturer's name, which is in darker print. The shiny foil label makes it especially difficult to read the print depending on how light hits the package. One reporter also stated that the printing rubs off so that some packages do not have the dosage strengths on the labels. Another reporter stated that some blister labels appear fainter than others. Secondly, the blister packs for both strengths are the same size with the same configuration of 14 tablets and an empty square in the middle of the blister pack. Although there is no tablet attached to the back of the empty square, it has been inadvertently mistaken for an actual square containing the drug. Furthermore, the strengths are barely distinguishable as printed on the aluminum foil-like packaging in small black type. Third, the tablets are essentially the same color and size to the naked eye. The imprints look very similar and it would be easy to mistake the "O" (1 mg imprint- TO) for a "D" (2 mg imprint- DT) or vice versa. In addition, the labeling on the Detrol 1 mg and Detrol 2 mg cartons are identical except that the 1 mg tablet strength is printed in blue and 2 mg strength is printed in magenta. Although most of the 16 reports are potential errors, actual errors occurred in 2 cases. However, no adverse events resulted since the errors were discovered prior to patient administration. In order to prevent future medication errors involving these two strengths, labeling changes are warranted as shown in section III of this review. *(See Appendix C for full-text narratives.)*

5. The alternate modifier, "LA" is also a known medical abbreviation for "long-acting" formulations and has been used in proprietary names such as Entex LA, Inderal LA, Inderide LA, and Exgest LA. However, since the modifiers for Detrol LA and Ditropan XL differ and do not pose a significant safety risk of name confusion at this time, the use of the term, "LA" for the proposed drug is not objectionable at this time.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton labeling, and the package insert of Detrol and OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container label, carton labeling, and the package insert and has identified an area of possible improvement, which might minimize potential user error.

A. CONTAINER LABELS

1. Detrol Blister Labels (1 mg & 2 mg)

a. As discussed in Section II C4 of this review, the blister labels are difficult to read due to the shiny aluminum foil-like packaging and the small print size. We recommend increasing the size of the blister labels and the font prints so that the information on the labels is easily readable. Furthermore, we do not recommend the use of aluminum-foil like material that hinders the legibility of the labels.

b. The blister labels for Detrol 1 mg and 2 mg strengths are almost identical except for the strengths of the tablets. In order to prevent potential dispensing errors between the two strengths, we recommend revising the blister labels so that they appear distinctively different. Moreover, we recommend increasing the prominence of the strength and decreasing the prominence of the manufacturer name so that the most prominent components of the labels are the name and strength of the product.

c. The blisters contain 14 tablets with an empty square in the middle of the pack. Although there is no tablet attached to the back of the empty square, it has been inadvertently mistaken for an actual square containing the drug and dispensed accordingly. We recommend that each square of the blister label contains the drug and is labeled appropriately.

d. One reporter stated that the printing rubs off the labels so that some packages do not have the dosage strength on the product. Another reporter stated that the some blister labels appear fainter than others. We recommend revising the labels so that they are always readable with the same print consistency.

2. **Detrol Container Labels (1 mg & 2 mg)**

a. We recommend that the established name be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g) (2).

b. Although the 1mg and the 2 mg strengths are printed in different colors, the distinction is not very apparent considering the identical design of the labels and the use of the same colors for the rest of the labels. We recommend revising the container labels so that the two strengths appear distinctively different.

c. If space permits, we recommend relocating the "Rx Only" statement to the front of the labels.

3. **Detrol XL Container Labels (2 mg & 4 mg)**

1. Having an overlapping strength (2mg) for two drug products with the same active ingredient and different pharmacokinetics is a known associated risk factor in dispensing and/or prescribing errors. Detrol and [redacted] fit this profile. In order to prevent dispensing errors between the two strengths, we recommend that the labels for Detrol and [redacted] appear distinctively different. Moreover, if colors are used to differentiate the various strengths, we recommend that the same colors are not used for Detrol and [redacted] labels.

2. As discussed in Section II C2 above, we recommend revising the established name to read, "tolterodine tartrate **extended-release** capsules."

B. **CARTON LABELING (Detrol 1 mg & 2 mg)**

1. On the *Sample Tray for Blisters*, ' [redacted] ' should be revised to read:

Professional Sample – Not for sale

In addition, we recommend including the strength of the product on this sample carton labeling.

2. See comments under CONTAINER LABEL.

C. **PATIENT INSERT (Detrol XL 2 mg & 4 mg)**

We recommend including the information regarding the difference between Detrol and [redacted] in the patient insert in order to inform patients transferring from Detrol or other agents to [redacted].

D. **PACKAGING (Detrol (1 mg & 2 mg)**

As previously discussed, both Detrol 1 mg & 2 mg tablets are white, round, biconvex, film-coated tablets engraved with arcs above and below the letter imprints. In order to prevent medication errors due to look-alike tablets, we recommend that these tablets appear distinctively different in color and design.

IV. RECOMMENDATIONS:

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

B. OPDRA recommends the above labeling revision that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3161.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 9/28/2000

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

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ON ORIGINAL

Appendix A

Medication Error Reports of Name Confusion Involving Detrol

The following narratives were transcribed from the medication error reports that were submitted. Therefore, the description of events may not be complete or relevant in all cases. Furthermore, since all reports do not provide the date of events, other dates (such as the date that the report was written or when it was received by the MedWatch/USP/ISMP) are listed below.)

1. ISR# 3539673-4 (Date of Event 3/17/00)
   After a patient presented a prescription for Detrol 2 mg, a pharmacy technician in training entered the prescription into the computer as Prandin 2 mg. The technician counted out Prandin 2 mg tablets and labeled the prescription vial as Prandin 2 mg. According to the reporter, the patient discovered the error, and the medication was not used. The pharmacist stated that she failed to perform an adequate final check of the prescription during a peak prescription time at a retail chain pharmacy, and that when the prescription was dispensed, she was not asked to counsel the patient.

2. ISR# 3392211-1 (Date of Event 6/99)
   A woman reported that her 7 year old daughter took 2 mg Detrol for 1 month by mistake when the pharmacy inadvertently dispensed Detrol. She said in looking back over the last month that she remembers her daughter asking for something for a headache, which was unusual. She also noticed her urine had a very strong odor which still persists after discontinuing the Detrol. The mother is pushing fluids and not giving her daughter any medication at the present time. No further information was provided.

3. ISR# 3309265-0 (Date of Event 4/12/99)
   A physician reported that a 16 year old boy with a history of head trauma, ADHD, and enuresis was prescribed DDAVP but was inadvertently dispensed Detrol by the pharmacy. He had taken Detrol 6 mg daily for a couple of weeks. He had trouble sleeping and recently been fighting with other children. Urinary retention was also noted by his physician and resolved upon drug discontinuation. No further information was provided.

   ISR# 3408593-8 (Date of Event 2/99)
   A woman reported that her husband was prescribed an unspecified medication and received Detrol instead. He used it for 2 weeks and started having muscle spasms. A follow-up phone conversation with the reporter was conducted on 9/12/2000. According to the reporter, the pharmacist should have dispensed an unspecified antibiotic, instead of a " Detrol-like drug" since the patient was already taking Detrol. A follow-up conversation with the pharmacist revealed that the patient came into the pharmacy with a prescription that contained two drugs, oxybutynin and Septra. The customer pointed to oxybutynin and asked that only this drug be filled since the other drug does not need to be filled at this time. The patient explained that she still had supplies of the other medication at home. The pharmacist correctly dispensed oxybutynin.

5. ISR# 3297963-7 (Date of Event 9/15/98)
   A physician reported a pregnant 25 year old female took 4 Detrol tablets when her prescription was erroneously filled. The woman was approximately 8-9 weeks pregnant with an estimated date of confinement of 4/21/99. She was given a prescription for an unspecified medication which was erroneously filled with Detrol and took 4 tablets the following day before discovering the error. When the prescription was erroneously filled with Detrol tablets, prenatal vitamins should have been dispensed. The gestational age of the fetus was 6.3 weeks by ultrasound. According to the physician, he saw the patient one time on 9/14/98, but on 10/21/98, she called to cancel her next appointment saying that she lost the baby. No further details provided.

Appendix B

Medication Error Reports Concerning [redacted]

1. ISR# 3484866-8 (Date of Report 3/20/00)
   A physician, who is the [redacted], reported that Pharmacia-Upjohn has submitted a new drug application for once daily Detrol to be called [redacted]. This raises great concern because of the existing product, Ditropan XL that is marketed also to patients with overactive bladder and is the primary competition for Detrol. Many of our patients that use these drugs are elderly and many of them are in institutionalized or assisted living communities. The dosages for these two

medicines are quite different, and some people may have allergic reactions to oxyoutynin or tolterodine and become confused and take the wrong medication because of the similar names. Even now we have patients who confuse Detrol with Ditropan XL. To allow labeling of the new Detrol once a day product as ——— would dramatically complicate this problem.

With the federal government being increasingly invested in trying to avoid such medication errors, I think it would be crucial to avoid such similarity in naming two different products used in the same patient population. I believe that I can represent the concerns of not only urogynecologists, but also urologists who are actively treating patients for overactive bladder.

2. ISR# 3484938-8 (Date of Report 3/18/00)
A physician, who is [redacted] reported that Pharmacia-Upjohn have placed a NDA for long-acting tolterodine (Detrol), and the potential name for the product is '———' This would be a terrible mistake. Ditropan XL is the only once-a-day anticholinergic on the market for overactive bladder symptoms. The potential confusion between brand names is obvious. The medical field already has a real problem with similarities between medication brand names. Why add to the problem? SR or CR for slow-release or controlled-release would imply the same drug benefit without brand confusion. I strongly urge you to prevent this problem before it has a chance to start.

3. ISR# 3484937-6 (Date of Report 3/17/00)
A physician, who is [redacted], reported that new once daily Detrol has been submitted by Pharmacia and Upjohn under the proposed brand name of [———] This name could present a problem with the already marketed product Ditropan-XL. In light of the potential for confusion and the resulting detrimental effects, the reporter suggested that FDA reject Pharmacia and Upjohn's request to name the new once daily tolterodine as ——— They could get the same point across by calling it Detrol SR, for sustained release or Detrol ER for extended release. This would do away with the problems that could exist in leading to a prescription error. Two drugs with the name Ditropan-XL and [———] spensing errors could cause some significant problems especially with respect to things such as the hypersensitivity to the drug. Both of these drugs are contra-indicated in persons with hypersensitivities to the active compounds and since the active compounds are different, potential harm to the patient exists. Other confusions relate to pregnancy categories where Ditropan XL has been classified pregnancy category B and Detrol has been classified pregnancy category C. Lastly, I want to bring to your attention that Ditropan XL is available in three dosage strengths (5, 10, and 15 mg and titration can come up to as high as 30 mg.) ——— apparently will come in two strengths 2 mg and 4 mg, and I can see how there could be pharmacy confusion as individual physicians titrate these drugs differently. Pharmacia and Upjohn certainly would get the same point across by naming the drug as suggested above.

Appendix C

Medication Error Reports of Labeling Confusion Involving Detrol

1. DQRS: U# 26946 (Date Received 7/12/00)
The printing on the very small-unit dose package is too light except for the manufacturer's name which is in darker print and not uniform. The shiny foil label makes it especially difficult to read the print. Additionally, the product is packaged in such a way that it is possible to dispense a unit-dose blister without dispensing the label. The medication was not given to the patient.

2. ISR# 3539677 (Date of Report 7/11/00)
According to the reporter, the foil on the Detrol Unit Dose packaging is hard to read depending on how the light hits the package. The printing is small and rubs off so that some packages do not have the dosage strength on the product. The reporter also notified Upjohn.

3. ISR# 3499769-2 (Date of Report 5/10/00)
The reporting pharmacist and his staff have found that the printing on the unit-dose blister tablets for both strengths of Detrol (1 mg & 2 mg) is very, very poor. The strengths are barely distinguishable as printed on the aluminum foil-like packaging in black type. The blister must be held at an angle in the light to first attempt to read it. It is very faint. Also, the tablet strength is printed in the smallest type on the blister label. The name of the drug and the name of the manufacturer are printed bigger and bolder. This is a med error waiting to happen. One pharmacist already averted one error by spotting the wrong strength tablet in a patient's unit dose cassette. To make matters worse, the tablets are essentially the same color and size to the naked eye. The blisters are very small, too. The reporter suggests increasing the size of the blister, which will yield a larger area for the information. Furthermore, make the strength larger-it's the most important piece of information. Can the strengths be further differentiated by other means? Both strengths have the same formats and colors.

4. DQRS: M# 129089 (Date Received 5/8/00)
The printing on the unit dose packaging of these products is very small and hard to read. Making it hard to determine the strength – 1 mg or 2 mg- the printing is small black lettering on a shiny silver foil background. The packaging also uses rough-surfaced plastic, making the printing even harder to read.

5. DQRS: U# 599 (Date Received 4/28/00)
Detrol 1 mg and 2 mg look-alike. Both are small white tablets. The 1 mg has an imprint "TLO" and the 2 mg has an imprint "DT". Both are difficult to see. The medication was not given.

6. ISR# 3499555-3 (Date of Report 4/27/00)
According to the reporter, both strengths of Detrol tablets (1 mg and 2 mg) look identical; the tablets are white, round, and the same size. The imprint on the 1 mg is "TO", while on the 2 mg tablet, the imprint is "DT". These imprints look very similar and it would be easy to mistake the "O" for a "D" or vice versa. Additionally, the blister pack is the same size with the same tablet configuration of 14 tablets with an empty square in the middle of the pack. The reporter recommends changing the color of one tablet strength to avoid the error of wrong dose administration.

7. ISR# 3501387-4 (Date of Report 4/25/00)
According to the reporter, there is a potential problem with Detrol. Both Detrol 1 mg and 2 mg packages and tablets are almost identical.

8. DQRS: U# 128691 (Date Received 2/23/00)
The darkness of the printing is uneven on the blister card labeling, especially affecting the left column of the blister sheet. The tablet strength is very light and barely legible. You can make out "mg", but not the "2". The 2 mg tablets closely resemble the 1 mg tablets in size and color. There is a potential for medication errors to occur.

9. ISR# 3385411-8 (Date of Report 10/13/99)
According to the reporter, the labeling on the Detrol 1 mg and Detrol 2 mg containers is identical except that the strength of the 1 mg tablet is printed in blue and 2 mg strength is printed in magenta. Both tablets are white and the same size; the 1 mg tablet is imprinted "OT" and the 2 mg tablet is imprinted "DT", which does not assist in identification because the "D" and "O" are difficult to differentiate. The reporter recommended changing the code and the color of the 1 mg tablet. Change the labels so that there is significant differences in color and design.

10. DQRS: M# 127907 (Date Received 6/23/99)
Detrol is available in two strengths, 1 and 2 mg tablets. The tablets are nearly identical in appearance, differing only in small embossed letters. It seems ludicrous that a color or size difference was not employed to help differentiate the two. The medication was not given.

11. DQRS: U# 26150 (Date Received 5/26/99)
Package labeling makes it difficult to distinguish between the 1 mg and 2 mg tablets. The labeling is black print on the silver foil packaging. In addition, the tablets are the same size and color. The medication was not given to the patient.

12. ISR# 3271056-1 (Date of Report 5/4/99)
According to the reporter, Detrol 2 mg was filled instead of Detrol 1 mg. The packages are identical except for the 1 and 2, but are very difficult to read because of the background and contrast. This error was caught before it went to the nursing unit. The error was discovered by a pharmacist during checking procedure for cart fill.

13. DQRS: M# 127708 (Date Received 4/21/99)
The tablet size, color, and markings on the Detrol 1 and 2 mg tablets are far too similar for safety. Without careful observation and a magnifying glass, it is extremely difficult to tell these two apart. We would prefer a color difference or some other obvious indication between the strengths of these tablets. The medication was not given.

14. ISR# 3249090-2 (Date of Report 4/16/99)
According to the reporter, Detrol 1 mg and 2 mg tablets are of similar size and shape. The imprint is also similar. When repackaged from bulk for long term care institutions in "bingo cards" it is easy to mistake them.

15. DQRS: M# 127394 (Date Received 1/22/99)
Detrol 1 mg and 2 mg tablet size, shape, and color are identical. Tablet markings are similar and difficult to see. High potential

for errors.

16. DQRS: U# 25748 (Date of Event 11/24/98)
Detrol 1 mg and 2 mg tablets have exactly the same appearance. They are the same color and have the same tablet markings.

CC:

NDA: 21-228
Office Files
HFD-580; DivFiles; Evelyn Farinas, Project Manager
HFD-580; Susan Allen, Division Director
HFD-400; Jerry Phillips, Associate Director, OPDRA

Electronic only cc:

HFD-002: Murray Lumpkin, Deputy Center Director for Review Management
HFD-400: Peter Honig, Director, OPDRA
HFD-040: Patricia Staub, Senior Regulatory Review Officer, DDMAC
HFD-440: Mary Dempsey, Project Manager, OPDRA
HFD-400: Sammie Beam, Project Manager, OPDRA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA J. Phillips att: Sammie Beam			FROM: Evelyn R. Farinas	
DATE: July 17, 2000	IND NO.:	NDA NO.: N21-228	TYPE OF DOCUMENT: Tradename request	DATE OF DOCUMENT: June 8, 2000
NAME OF DRUG: Tolterodine extended release	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG: GU	DESIRED COMPLETION DATE: September 15, 2000

NAME OF FIRM: Pharmacia and Upjohn

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☒ OTHER *(SPECIFY BELOW)*:
Tradename review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: cc:

SIGNATURE OF REQUESTER: /S/	METHOD OF DELIVERY (Check one): MAIL ☒ HAND
SIGNATURE OF RECEIVER: /S/ 7-18-00	SIGNATURE OF DELIVERER:

Pharmacia & Upjohn

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

June 8, 2000

DUPLICATE

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

NEW CORRESP
NC

RE: NDA 21-228
Tolterodine ——— release capsules

General Correspondence
Request for Comment

Dear Sir/Madam:

As we have now completed our internal reviews and assessment, we request feedback from the Agency on the acceptability of ——————— as our primary choice for the trademark for the above referenced product.

As a back-up choice we propose DETROL™ LA.

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 G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:lmf

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 09 2000
HFD-580

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

AIP Integrity Policy

This application is not on the AIP.

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Post Marketing Commitments

Not applicable for this submission.

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

Press Office information

Not applicable for this application; Press Office notified.

APPEARS THIS WAY
ON ORIGINAL

c0020976

NDA 21-228
Tolterodine [redacted] Release Capsules

PATENT INFORMATION / PATENT CERTIFICATION

1.	Active Ingredient	Tolterodine L-tartrate
2.	Strength(s)	2 and 4 mg
3.	Trade Name	Detrol
4.	a. Dosage Form	[redacted] Release Capsules
	b. Route of Administration	Oral
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	21-228
7	NDA Approval Date	To be determined
8.	Applicable patent numbers and expiration date of each	5,382,600 Claims cover 3,3-diphenylpropylamines, including tolterodine, and pharmaceutical compositions comprising them. 5,922,914 Expiration date – December 18, 2017 Claims cover a process for producing tolterodine-L-tartrate

This to certify that the above information is correct to the best of my knowledge.

Annika Ohlsson
Director Regulatory Affairs
Pharmacia & Upjohn AB, Sweden

EXCLUSIVITY SUMMARY for NDA # 21-228 SUPPL # _____

Trade Name Detrol LA Generic Name tolterodine extended release

Applicant Name Pharmacia & Upjohn HFD- 580

Approval Date December 22, 2000

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/ X / NO /___/

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

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

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 /X/ NO /___/

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 /___/ NO /X/

If yes, NDA # _____ Drug Name _____

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 /X/

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 /X / NO / _/

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

NDA # _____ _____

NDA # NDA 20-771 _____

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 <u>any one</u> 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 /_ _/

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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 /X/ 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 /X/ 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 /X/

(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 /X/

If yes, explain: _____

_____

APPEARS THIS WAY
ON ORIGINAL

(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 /X/

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 # 98-TOCR-007

Investigation #2, Study # 98-TOCR-007B

Investigation #3, Study # 97-TOCR-002

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

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 /X/

Investigation #2 YES /___/ NO /X/

Investigation #3 YES /___/ NO /X/

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 #1, Study # 98-TOCR-007

Investigation #2, Study # 98-TOCR-007B

Investigation #3, Study # 97-TOCR-002

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 # _____ NO /___/ Explain: _____

_____

_____

Investigation #2

IND _____ NO /___/ Explain: _____

_____

Investigation #3

IND _____

_____

(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 /_x_/

If yes, explain: _____

_____

_____

/S/

Signature of Preparer

12/22/00

Date

Title: Project Manager

/S/

Signature of Office of Division Director

12/22/00

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

APPEARS THIS WAY
ON ORIGINAL

DEBARMENT CERTIFICATION FOR TOLTERODINE [redacted] Release Capsules
NDA # 21-228

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

01/04/2000

Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

Date

APPEARS THIS WAY
ON ORIGINAL

Pharmacia&Upjohn

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

April 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

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

Amendment #3

Dear Sir/Madam:

It has come to our attention (through a telephone contact from Lana Pauls at FDA) that FDA form 3454 was provided in the Financial Disclosure (Item 19) section of the above NDA in error. Two investigators did in fact disclose a financial interest and a FDA form 3455 was also completed and included in the NDA. Pharmacia & Upjohn is therefore requesting that the FDA form 3454 (found in Volume 1.1, page 10) be withdrawn.

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 G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS:mlw

cc Lana Pauls HFD-580

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. XXXX-XXXX Expiration Date: xx/xx/xxxx
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Re: Tolterodine Tablets/Capsules

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further clarify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Name Gunnar Casserstedt	Title Vice President, R&D Finance
Firm/Organization Pharmacia & Upjohn	
Signature	Date 12/15/99

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Paperwork Reduction Project (0910-xxxx)
Humphrey Building, Room 531-H
200 Independence Ave., SW
Washington, DC 20201

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

Please DO NOT RETURN this application to this address

FORM FDA 3454 (7/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: xx/xx/xxxx

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Re: Tolterodine Tablets/Capsules

TO BE COMPLETED BY APPLICANT

The following information concerning Dr. Simon Hill & Dr. Robert Freeman, who participated as a
Name of clinical investigator

clinical investigator in the submitted study Tolterodine Tablets/Capsules, is submitted in
Name of clinical study

accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkbox

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study.

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

see attached Data Integrity Assurance Factors

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b) held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests

Name Gunnar Casserstedt	Title Vice President, R&D Finance
Firm/Organization Pharmacia & Upjohn	
Signature	Date 12/15/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

← Please DO NOT RETURN this application to this address

FORM FDA 3455 (10/98)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

2 Pages

Data Integrity Assurance Factors for Investigators Disclosing Financial Interest

Protocol 98-TOCR-007 was a double-blind (double-dummy technique), randomized, placebo-controlled, multi-center and multi-national study enrolling 1529 patients (507 on Tolterodine [redacted] Release, 514 on Tolterodine Immediate Release and 508 on placebo) from 167 centers in 14 countries.

Controls in place to ensure data integrity

- All study centers were monitored regularly and Source Data Verification was done and documented according to GCP.
- The statistical analysis did not show any country effects.
- All study personnel were blind to treatment throughout the study.

Dr. Simon Hill, MD

- Dr. Hill enrolled 7 patients in the study.
- Monitoring visits were done approximately every 4 weeks. SDV was done to some extent at each visit.
- The site had an average number of audits.
- There was no audit done at this center.

Dr. Robert Freeman, MD

- Dr. Freeman enrolled 17 patients in the study.
- Monitoring visits were approximately done every 4 weeks. SDV was done at some extent at each visit.
- The site had an average number of audits.
- Audit was done at this center.

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

52 pages

DUPLICATE

Pharmacia & Upjohn

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

December 15, 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

N000-150

RE: NDA 21-228
Tolterodine extended release capsules

Amendment # 14

Dear Sir/Madam:

Reference is made to the chemistry reviewer's requests that you relayed to Pharmacia & Upjohn in the telephone contact of December 12,2000.

Pharmacia & Upjohn commits to having complete NDC numbers in the how supplied section of the package insert.

Pharmacia & Upjohn commits to having complete lot and expiration date information on all primary and secondary product packaging.

Non-insert labeling using the [redacted] along with non-insert labeling using the LA suffix was submitted in Amendment 12. Please [redacted] as we have been informed by the Division that this suffix will not be approved.

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:SEH

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-228

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmacia & Upjohn Company	December 15, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(616) 833-6579	(616) 833-8237

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

7000 Portage Road
Kalamazoo, Michigan 49001

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* USAN:	PROPRIETARY NAME *(trade name)* IF ANY
Tolterodine Release Capsules	To Be Determined

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (R)-N,N-Diisopropyl-3-(2-hydroxy-5-methylpheynl)-3-phenyl propanamine L-hydrogen tartrate

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	2mg and 4mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Indicated for the treatment of

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505-(b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telepone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Nordic Synthesis AB	Pharmacia & Upjohn	Pharmacia & Upjohn Caribe Inc.
Bjorkborn Industrial Area	7171 Portage Road	Road #2 KM 60.0
S-691 85 KARLSKOGA Sweden	Kalamazoo, MI 49001 USA	Barceloneta, Puerto Rico 00617

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

PHARMACIA & UPJOHN, INC. FACSIMILE

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

TO: Evelyn Farinas

DATE: December 13, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA -21-228

FROM: Gregory Shawaryn
PHONE: 616-833-8239

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

Message:

Dear Evelyn,

Reference is made to the chemistry reviewer's requests that you relayed to Pharmacia & Upjohn in the telephone contact of December 12,2000.

Pharmacia & Upjohn commits to having complete NDC numbers in the how supplied section of the package insert.

Pharmacia & Upjohn commits to having complete lot and expiration date information on all primary and secondary product packaging.

Non-insert labeling using the [redacted] along with non-insert labeling using the LA suffix was submitted in Amendment 12. We fully intend [redacted] once a clearer understanding of the status of the review of the [redacted] trademark proposal is obtained.

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

Sincerely,

Gregory Shawaryn

** TOTAL PAGE.001 **

Pharmacia&Upjohn

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

December 13, 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 21-228
Tolterodine extended release capsules

Amendment # 13

Dear Sir/Madam:

It has come to our attention that the exclusivity request was inadvertently omitted from the original submission of the above NDA. Enclosed please find Pharmacia and Upjohn's request for exclusivity for the above product.

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 G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS/crdt

Enclosures

REQUEST FOR EXCLUSIVITY

Pharmacia & Upjohn Company requests three (3) years of exclusivity for tolterodine extended release capsules pursuant to 21 U.S.C. 355 (c)(D)(iii). The following is provided to assist FDA in the eligibility determination. This summary information follows the basic format contained in the letter of April 28, 1998 from Dr. Carl Peck to all NDA or ANDA Holders and Applicants.

1. This application contains reports of clinical investigations.
2. The clinical investigations included in this application were conducted specifically to document the safety and efficacy of tolterodine extended release capsules.

   Specific Protocols conducted to support this application:

   97-TOCR-001
   97-TOCR-002
   97-TOCR-003
   98-TOCR-005
   98-TOCR-006
   98-TOCR-007
   98-TOCR-007B
   98-TOCR-0010

3. Without the above studies safety and efficacy of this product could not be supported.
4. Pharmacia and Upjohn was the sponsor of these studies and of the IND supporting this NDA.

Exclusivity requested is for three years after the date of NDA approval, or December 18, 2017 or date of any patent extension--whichever occurs last.

Mark Mannebach
Associate Director
Regulatory Affairs

12/13/00
Date

PHARMACIA & UPJOHN, INC. FACSIMILE

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

TO: Evelyn Farinas **DATE:** December 13, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA -21-228

FROM: Gregory Shawaryn
PHONE: 616-833-8239

TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 3

Message:

Dear Evelyn,

Attached please find our exclusivity request for the above mentioned product/NDA. It is being sent hardcopy today as well.

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

Sincerely,

Greg Shawaryn

Gregory Shawaryn

Pharmacia&Upjohn

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

ORIGINAL

December 7, 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

ORIG AMENDMENT

BC

RE: NDA 21-228
Tolterodine extended release capsules

Amendment # 12

/s/

Dear Sir/Madam:

Reference is made to the Division's 11/22/00 request for information relative to the chemistry review of the above application.

Requests/Comments 1 through 4 are addressed in Attachment 1. The updated Methods Validation Package is included in triplicate in 3 separate volumes.

With regard to Point 5 (a-d): Requests/Comments are addressed in Attachment 2. This package insert also contains Pharmacia & Upjohn (P&U) comments addressing the proposed package insert faxed by the Division to P&U on 11/27/00. An electronic version is also being submitted today via secure e-mail to farinase@cder.fda.gov.

With regard to Point 5e: Mock-up labeling for the following is included in Attachment 3 (labels using the suffix LA and

Unit Dose Blister Card 4 mg (card of 10 capsules)
NDC 0009-5191-04--Copy Code 818 233 000
Carton for Unit Dose Cards 4mg (100 capsules)
NDC 0009-5191-04--Copy Code 818 234 000

Unit Dose Blister Card 2 mg (card of 10 capsules)
NDC 0009-5190-04--Copy Code 818 230 000
Carton for Unit Dose Cards 2mg (100 capsules)
NDC 0009-5190-04--Copy Code 818 231 000

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Bottle Label 4mg (500 count bottle)
NDC 0009-5191-03--Copy Code 818 272 000

Bottle Label 2mg (500 count bottle)
NDC 0009-5190-03--Copy Code 818 270 000

Bottle Label 4mg (90 count bottle)
NDC 0009-5191-02--Copy Code 818 267 000
Carton Label 4mg (90 count bottle)
NDC 0009-5191-02--Copy Code 818 268 000

Bottle Label 2mg (90 count bottle)
NDC 0009-5190-02--Copy Code 818 261 000
Carton Label 2mg (90 count bottle)
NDC 0009-5190-02--Copy Code 818 262 000

Bottle Label 4mg (30 count bottle)
NDC 0009-5191-01--Copy Code 818 264 000
Carton Label 4mg (30 count bottle)
NDC 0009-5191-01--Copy Code 818 265 000

Bottle Label 2mg (30 count bottle)
NDC 0009-5190-01--Copy Code 818 257 000
Carton Label 2mg (30 count bottle)
NDC 0009-5190-01--Copy Code 818 258 000

Sample Foil Label 4mg (7 count blister card)
NDC 0009-5191-99--Copy Code 818 463 001

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 G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS/crdt

Attachments

PHARMACIA & UPJOHN, INC. FACSIMILE

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

TO: Biopharm reviewer NDA 21-228 C/O Evelyn Farinas **DATE:** November 13, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA -21-228

FROM: Gregory Shawaryn
PHONE: 616-833-8239

TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 3

Message:

Attached is the information requested by the biopharm reviewer regarding PK calculations included in the proposed PI. Hardcopy is also being sent today.

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

Sincerely,

Gregory Shawaryn

Gregory Shawaryn

APPEARS THIS WAY
ON ORIGINAL