Pharmacia&Upjohn

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

November 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 [redacted]
release capsules

Amendment # 11

Dear Sir/Madam:

On November 3, 2000, via telephone contact, the Division posed the following request.

In the proposed package insert, please clarify how the PK parameters were calculated, especially the single dose data included in Table 1. If the calculation is included in the NDA please provide the location, if not, please submit the calculation.

Please find in Attachment 1 the calculations and location of data in the NDA associated with these calculations.

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

Attachment

Attachment 1

The pharmacokinetic parameters presented in Table 1 in the Package Insert were calculated as follows:

C_{max} for the single-dose is C_{max} reported in study 010 divided by 2, to normalize it to a 4-mg dose (studied dose was 8 mg).

C_{avg} for the single dose is AUC_{∞}, from the report for study 010, divided by 2, to normalize it to a 4-mg dose, and then divided by 24.

C_{avg} for the multiple dose is AUC_{24}, from the report for study 006, divided by 24.

All other parameters are presented as reported in studies 006 (page 6/6/94 of the NDA) and 010 (page 6/7/136 of the NDA), although in some instances with fewer decimals than in the original reports.

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Pharmacia & Upjohn

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

November 3, 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

Sel Chemists Review
#1
/S/
14-NOV-2000

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

Amendment # 10
Authorization to Cross-Reference
Supplement S-003

Dear Sir/Madam:

In response to the Division's November 2, 2000 request, Pharmacia & Upjohn authorizes reviewers of the above NDA to cross-reference Supplement S-003 of NDA 20-771.

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:kmv

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

DUPLICATE

Pharmacia&Upjohn

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

October 30, 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
BM

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

Amendment # 9
Response to FDA Request

Dear Sir/Madam:

Reference is made to the October 26, 2000 request to confirm that the formulation of extended release tolterodine used in the clinical trials is exactly the same as the to be marketed formulation.

Attached is the requested confirmation.

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

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:kmv

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	October 30, 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 [redacted] 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 patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

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
Amendment #9

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.

[redacted]	Pharmacia & Upjohn 7171 Portage Road Kalamazoo, MI 49001 USA	Pharmacia & Upjohn Caribe Inc. Road #2 KM 60.0 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)

Tolterodine [redacted] -Release Capsules:
Question from FDA Biopharmaceutics Reviewer
(I2000-132)

Provide written confirmation that the formulation of extended release tolterodine used in the clinical trials is exactly the same as the to be marketed formulation.

The [redacted] formulation used in the primary safety/efficacy study (protocol 98-TOCR-007) is identical to the formulation intended for the market. The finished capsules differ only in color: yellow capsules were used in the clinical study, while blue (4 mg) and blue-green (2 mg) capsules will be used for the marketed product.

Other formulations were explored during the clinical program. All formulations are fully described in section 8, "Investigational Formulations", of the CMC Summary and are cross-referenced to the clinical study in which they were used.

Pharmacia&Upjohn

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

NEW CORRESP DUPLICATE

October 25, 2000

Dr. Roy Blay
Office of Medical Policy, DSI, GCP Branch 1
HFD-46
7520 Standish Place
Rockville, MD 20855

RE: NDA 20-771/ S-004

APPEARS THIS WAY ON ORIGINAL

[redacted] Detrol™
Tolterodine tartrate tablets
And [redacted] release capsules

Requested Patient Diaries

Dear Dr. Blay:

In response to your October 17 request, please find patient diaries for Dr. Freedman's site, collected in association with his participation in 98-TOCR-007.

A listing of the diaries included in this submission is attached.

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
Global Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

GGS:lmf

Attachment

cc: Division of Division of Reproductive Health and Urologic Drug Products HFD-580

List of Micturition Charts (originals and copies) from center 219, Dr. Sheldon Freedman.

		Micturition Chart	
Center no.	Patient no.	Visit 2	Visit 4
219	1199	X	-
219	1200	X	X
219	1201	X	X
219	1202	X	X
219	1203	X	X
219	1204	X	X
219	1433	X	X
219	1434	X	X
219	1435	X	-
219	1436	X	X
219	1437	X	X
219	1438	X	X
219	1511	X	X
219	1512	X	X
219	1513	X	X
219	1553	X	-
219	1554	X	X
219	1555	X	X
219	1556	X	X
219	1557	X	X
219	1558	X	X
219	1559	X	X
219	1560	X	X
219	1561	X	X
219	1562	X	X
219	1563	X	X
219	1564	X	-
219	1598	X	X
219	1599	X	X
219	1600	X	X
219	1867	X	X
219	1931	X	X
219	1932	X	-
219	1933	X	X
219	1934	X	X
219	1935	X	X
219	1936	X	X
219	1937	X	X
219	1938	X	X
219	1939	X	X

PHARMACIA & UPJOHN, INC. FACSIMILE

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

TO: Evelyn Farinas

DATE: September 7, 2000

FACSIMILE # 301-827-4267

SUBJECT: [redacted]

FROM: Gregory Shawaryn
PHONE: 616-833-8239

TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 5

Message:

Dear Evelyn,

In response to you request for clarification regarding "estimation" of micturition data in protocol 98-TOCR-007, please find the attached explanation of how the estimation/calculation was performed and listings of patients for which the calculation was performed.

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

Sincerely,

Gregory Shawaryn

APPEARS THIS WAY
ON ORIGINAL

According to the protocol, the micturition diary should be completed at least five days of out of seven, when calculating (estimating) the efficacy variables mean number of incontinence episodes per week, mean number of micturitions per 24 hours and proportion of micturitions associated with urgency. For mean volume voided per micturition and mean number of pads per 24 hours, measurements should be completed for at least two days.

The following sentence was added in amendment 4 to the study protocol: *"If micturition chart diaries are not completed according to the protocol, the estimations of the micturition variables will be based on the available data."*
This means that if a patient had completed the micturition diary for less than five days, then mean number of incontinence episodes per week was calculated (estimated) based on those days the micturition diary was completed. For example, if a patient only completed the diary for four days, then the mean number of incontinence episodes / week for this patient was calculated as(estimated to be) seven times number of incontinence episodes during 4 days / 4. This is analogous for all micturition variables.

A list of all subjects for whom the efficacy variables was calculated (estimated) based on data for less than 5 days, including the actual visit and number of completed days, is provided as requested.

As already indicated, "estimated" means calculated in this case. We admit that calculate would have been a more appropriate word.

Pharmacia & Upjohn, CTN: 98-TOCR-007 1
Listing of Subjects and Visits Where Micturition Chart Diary Was Completed for Less Than 5 Days.
Treatment: Placebo

Patient	Visit 2 Days Complete	Visit 4 Days Complete
1085	2	
1098		2
1193	3	
1235	2	2
1392		4
1577	2	
1592		2
1597		2
1659	2	
1660	2	
1682	2	2
1696	2	
1984		2
2511		3
2535	3	
2926		2

Pharmacia & Upjohn, CTN: 98-TOCR-007 2
Listing of Subjects and Visits Where Micturition Chart Diary Was Completed for Less than 5 Days.
Treatment: Tolterodine 4 mg q.d

Patient	Visit 2 Days Complete	Visit 4 Days Complete
1481		2
1482		2
1494	2	
1535	4	
1568		4
1595		4
1653		2
1658	2	
1704	2	2
1911		4
1979	3	
2343	4	
2810		2
2955	2	
3018		3
3202		2
3219		4
3396		3

Pharmacia & Upjohn, CTN: 98-TOCR-007
Listing of Subjects and Visits Where Micturition Chart Diary Was Completed for Less Than 5 Days.
Treatment: Tolterodine IR 2 mg b.i.d

Patient	Visit 2 Days Complete	Visit 4 Days Complete
1007	2	
1088	2	
1109		2
1263	2	
1391		2
1493	2	
1578	4	
1649		2
1874		1
1880	2	
1916		4
2274		1
2351		2
2355	4	
2493		4
2524		3
2640		4
3221		4

APPEARS THIS WAY
ON ORIGINAL

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: [redacted]
Tolterodine [redacted] 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 [redacted] 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

APPEARS THIS WAY
ON ORIGINAL

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

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Pharmacia & Upjohn Company

2. DATE OF SUBMISSION
August 21, 2000

3. ADDRESS *(Number, Street, City, State and Zip Code)*
7000 Portage Road
Kalamazoo, Michigan 49001

4. TELEPHONE NUMBER *(Include Area Code)*
(616) 833-8239

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
PNU-200583

6. IND NUMBER *(If previously assigned)*
[redacted]

7. INDICATION(S) *(Covered by this submission)*
[redacted]

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER: _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
NDA 20-771

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER: 040

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☒ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

Pharmacia & Upjohn 98-TOCR-007
Urology

AMENDMENT ID & DATE: #4 02 July 1999

AMENDMENT STATUS: Final

PRODUCT: Tolterodine [redacted] release capsules)

PROTOCOL No: 98-TOCR-007

PROTOCOL DATE: 30 October 1998

PROTOCOL TITLE: Clinical efficacy and tolerability/safety of tolterodine [redacted] release capsules and tolterodine immediate release tablets vs placebo. A randomized, double-blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder.

Trial Conduct Team Leader
Marion Stamp-Cole, B.S.
Clinical Trials Specialist
Pharmacia & Upjohn
1029-243-138
7000 Portage Road
Kalamazoo, MI 49001-0199

Phone: 616-833-8243
Fax: 616-833-8004

Marion Stamp-Cole 07/13/99
Signature Date

Principal Investigator
Signature Date

Clinical Study Team Leader
Johan P. Söderström, M.Sc.
Clinical Trial Specialist
Pharmacia & Upjohn AB
SE-112 87 Stockholm, Sweden
Telephone: +46 8 695 4894
Facsimile: +46 8 695 4643

Johan Söderström 1999-07-08
Signature Date

Amendment Summary

Five centers in the Russian Federation and Ukraine will enroll approximately 60 subjects to compensate for non-performing centers. The statistical and analytical plans are updated in response to suggestions from the FDA. An ANOVA will replace the t-test. Also some clarifications are made.

Specific Protocol Text Changes (New text appear in italics)

1. 1 SUMMARY, protocol pages 6(41), 7(41), 9(41), 10(41)
Reason for change: To include changes from subsequent protocol sections.

a. Change under **Statistical methods:**
From: For the primary efficacy variable the t-test will be used to test the null hypothesis unless assumption of normal distributed data is violated. If that is the case the Wilcoxon rank sum test will be used instead.
To: *An ANOVA with treatment, center, and treatment by country as factors will be used to test the null hypothesis for the primary endpoint. In the case the assumption of normal distributed data is violated non-parametric methods will be used instead.*

b. Change under **SUBJECT POPULATION**
From: #Market companies: 11
To: #Market companies: *12*

c. Change in Schedule of events table
From: f) Subjects in the Netherlands, Norway and Flemish subjects in Belgium will only complete the SF-36.
To: f) Subjects in the Netherlands, Norway, *the Russian Federation, Ukraine,* and Flemish subjects in Belgium will only complete the SF-36.

d. Change in PARTICIPATING MARKET COMPANIES table

From:	**Market company**	**#Subjects**	**#Investigators**
	...	...	...
	Norway	48	5
	UK/Ireland	196	24
	...	...	...
To:	**Market company**	**#Subjects**	**#Investigators**
	...	...	...
	Norway	48	5
	Russian Federation/Ukraine	*60*	*5*
	UK/Ireland	196	24
	...	...	...

Note: The total number of subjects should remain unchanged (ALL=1350).

2. 2 ABBREVIATION AND DEFINITION OF TERMS, protocol page 10(41)
Reason for change: To include new abbreviation.

a. Change
From: -
To: ANOVA Analysis of variance

3. 5.1 Duration / Schedule of Events, protocol pages 16(41), 17(41), 18(41)
Reason for change: The King's Health Questionnaire (appendix 6) is not available in Russian. Subjects in the Russian Federation and Ukraine will not complete the King's Health Questionnaire.

a. Change under **Visit 2 (Inclusion)**
From: The subject completes QoL questionnaires (King's Health Questionnaire and SF-36. Subjects in the Netherlands, Norway and Flemish subjects in Belgium will only complete the SF-36).
To: The subject completes QoL questionnaires (King's Health Questionnaire and SF-36. Subjects in the Netherlands, Norway, *the Russian Federation, Ukraine,* and Flemish subjects in Belgium will only complete the SF-36).

b. Change under **Visit 4 (End of treatment, after 12 weeks ± 4 days on treatment or withdrawal)**
From: The subject completes QoL questionnaires (King's Health Questionnaire and SF-36. Subjects in the Netherlands, Norway and Flemish subjects in Belgium will only complete the SF-36).
To: The subject completes QoL questionnaires (King's Health Questionnaire and SF-36. Subjects in the Netherlands, Norway, *the Russian Federation, Ukraine,* and Flemish subjects in Belgium will only complete the SF-36).

c. Change in Schedule of events table
From: f) Subjects in the Netherlands, Norway and Flemish subjects in Belgium will only complete the SF-36.
To: f) Subjects in the Netherlands, Norway, *the Russian Federation, Ukraine,* and Flemish subjects in Belgium will only complete the SF-36.

4. 7.4 Blinding, protocol page 24(41)
Reason for change: To clarify.

a. Change

From: When the Clinical Study Team has reached a final decision regarding subject classification into different analysis categories the database is locked.

To: When *all data have been entered, and checked for correctness, and* the Clinical Study Team has reached a final decision regarding subject classification into different analysis categories the database is locked.

5. 8.1.1 Micturition chart, protocol page 27(41)

Reason for change: To clarify.

a. Change

From: Mean number of incontinence episodes per week.

To: Mean number of incontinence episodes per week*.

b. Change

From: -

To: Footnote is inserted to explain how mean number of incontinence episodes per week is calculated: * *Average number of incontinence episodes/day* $\times 7$.

c. Change

From: All efficacy variables are averaged for a minimum of five completed days, except mean volume voided per micturition and number of pads used, that are averaged for two days.

To: All efficacy variables are averaged for a minimum of five completed days, except mean volume voided per micturition and number of pads used, that are averaged for *a minimum of* two *completed* days.

6. 10 STATISTICS, protocol pages 37(41), 38(41)

Reason for change: To update and clarify the statistical and analytical plans as suggested by the FDA.

a. Change

From: The two-sided t-test will be used to test the null hypothesizes unless assumption of normal distributed data is violated. If that is the case the Wilcoxon rank sum test will be used instead.

To: *The null hypothesizes will be tested with the following ANOVA:* $Y=\mu+T+C+T*C+\varepsilon$, *where Y = change in mean number of incontinence episodes/week, T=treatment, C=Country and T*C=treatment by country interaction. The reason for choosing country as factor instead of center is due to expected low numbers of subjects in most centers. If the assumption of normally distributed data is violated, non-parametric methods will be used instead.*

b. Change

From: Corresponding 97.5% confidence intervals will also be calculated to describe the magnitude of treatment effects for both active treatment groups compared with placebo.

To: Corresponding 97.5% confidence intervals *based on the least square means from the ANOVA* will be calculated to describe the magnitude of treatment effects for both active treatment groups compared with placebo.

c. Change

From: Subgroup analyses on micturition variables will be made on subjects aged 65 years or older and subjects below 65 years.

To: Subgroup analyses on micturition variables will be made *with respect to age (<65/≥65 years), sex, and race.*

d. Change

From: New sentence inserted under 1. Intention-to-treat population after the last sentence.

To: *If micturition chart diaries are not completed according to the protocol, the estimations of the micturition variables will be based on the available data.*

Pharmacia & Upjohn

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

June 30, 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 [redacted] release capsules

Amendment # 6
Stability Update

Noted
See Chemistry Review #1.
[S]
10-31-00

Dear Sir/Madam:

Enclosed please find the following CMC information to update the above referenced NDA:

Attachment 1: Update to the stability database.
Attachment 2: Description, rationale and support for addition of an [redacted] machine.
Attachment 3: Addition of [redacted], a contract laboratory, for [redacted]

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:lmf

Attachments

(10/31/00 NAI - per ... entered into PFS 11/1/00 BSG

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
11-01-00
CSO INITIALS DATE

ORIGINAL

Pharmacia & Upjohn

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

June 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

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

ORIG AMENDMENT
PG

Amendment # 5
Proposed Pediatric Study Request

Dear Sir/Madam:

Reference is made to the Division's March 1, 2000 correspondence acknowledging receipt of the above referenced NDA. In that correspondence, the Division indicated that per 21 CFR 314.55 a description of our pediatric study plans needed to be submitted to this NDA.

In Attachment 1 we have provided a Proposed Pediatric Study Request which contains synopses of two protocols (583-EURO-0084-018 & 020) we are proposing in order to obtain a Written Request from the Division to qualify for pediatric exclusivity. These studies, previously submitted on April 12, 2000 to NDA 20-771, have been modified based upon discussions held with the Division on May 15, 2000. Protocol 020,previously submitted as protocol 98-AOTA-061, has been renamed for administrative reasons.

These studies also comprise the **pediatric study plan** for this formulation of Tolterodine.

Please note that this study plan includes patients aged 5 to 15 years. We request a partial waiver from pediatric study requirements for patients younger than 5 years old for the following reasons:

1. Children less than 5 years old cannot be expected to have developed full control of their bladder function.

2. Overactive bladder is not readily diagnosed in children less than 5 years old.

3. Uncertainty of diagnosis of overactive bladder in children less than 5 years old does not justify pharmacological treatment for overactive bladder.

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

10/18/00
See attached
Review
with
comments
for Sponsor
BSG

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL

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	June 28, 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 [redacted] 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 [redacted]

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
Amendment #5, Proposed Pediatric Study 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.

[redacted] .en	Pharmacia & Upjohn 7171 Portage Road Kalamazoo, MI 49001 USA	Pharmacia & Upjohn Caribe Inc. Road #2 KM 60.0 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)

Proposed Pediatric Study Request--Tolterodine

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

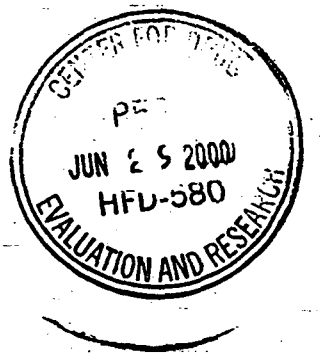
8 pages

Pharmacia & Upjohn

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

ORIGINAL

June 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

ORIG AMENDMENT
SU

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

Amendment #4
4-Month Safety Update

Dear Sir/Madam:

In accordance with 21 CFR 314.50, Pharmacia & Upjohn is providing the enclosed update of safety information to the above NDA. This submission contains an interim report on the long term continuation of protocol 98-TOCR-007B. The report contains information on 106 patients completing 12 months and 875 patients completing 6 months of treatment.

An electronic copy of Item 12 is included on compact disk. It is 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 151 megabytes. These files have been scanned with Network Associates' McAfee Virus Scan software for Windows, version 4.03. All electronic information is contained in the directory N21228 and a copy of this letter and the 356H form are also provided as a PDF files (cover.pdf and 356H.pdf respectively) in this directory.

Attachment 1 contains an abbreviated Table of Contents(TOC) for the amendment and is also provided as a PDF file (ndatoc.pdf) in directory N21228.

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

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:lmf
Attachment

REVIEW COMPLETED
CDD ACTION:
☐ LETTER ☐ E.A.L ☐ MEMO
CDD INITIALS DATE

(11/28/00) Reviewed in MO review of NDA 21-228 Submission 000 BSG

Attachment 1

Item 9	Safety Update	Paper
Item 12	Case Report Forms	Electronic

APPEARS THIS WAY
ON ORIGINAL

Pharmacia & Upjohn

Tolterodine [redacted] release capsules

(tolterodine L-tartrate)

NDA 21-228

4-month Safety Update

Data cut-off date: 30 April 2000

Pharmacia & Upjohn c0026978

PNU-200583/ Tolterodine [redacted] CLINICAL RESEARCH PNU-583-URO-0084 15 June 2000

Interim report on 12 months and 6 months safety data

Long-term safety and efficacy of tolterodine [redacted] release capsules. An open-label, uncontrolled, multinational study in subjects with symptoms of overactive bladder

Interim Report of the Trial
98-TOCR-007B

It is the policy of Pharmacia & Upjohn to conduct clinical trials in compliance with company SOPs and Standards which incorporate the requirements of the ICH Guideline for Good Clinical Practice. These include trial conduct and archiving of essential documents.

Trial Completion Date	TBD
Development Phase of Trial	Phase III
Authors of the Report	Helena Eriksson, B.Sc. Johan Szamosi, M.Sc. Urban Olsson, B.Sc.

Pharmacia & Upjohn c0026978

1 SIGNATURE PAGE

(Appendix 1 contains the scanned image of the approval signatures for this document. All original paper signature pages are retained in the paper document and kept in the paper document archive.)

Study Management Leader
Helena Eriksson, B.Sc.
General Medicine
Clinical Research, R&D
Pharmacia & Upjohn
Sweden

Signature Date

Statistician
Johan Szamosi, M.Sc.
Biostatistics and Data Management
Clinical Research, R&D
Pharmacia & Upjohn
Sweden

Signature Date

Data Management
Urban Olsson, B.Sc.
Biostatistics and Data Management
Clinical Research, R&D
Pharmacia & Upjohn
Sweden

Signature Date

Therapeutic Area Clinical Director
Elisabet Lindberg, M.D.
General Medicine
Clinical Research, R&D
Pharmacia & Upjohn
Sweden

Signature Date

2 TABLE OF CONTENTS

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LIST OF TABLES

APPENDICES

3 ABBREVIATIONS AND DEFINITION OF TERMS

bid	Twice daily
CRF	Case Report Form
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional Review Board
PR	Prolonged release
qd	Once daily
SD	Standard deviation
Study 007	Study 98-TOCR-007
Study 007B	Study 98-TOCR-007B

4 ETHICS

4.1 Independent Ethics Committee/Institutional Review Board

The protocol for this trial was reviewed and approved by the appropriate Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs).

4.2 Ethical Conduct of the Study

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5 INVESTIGATORS

The placebo-controlled study 98-TOCR-007 that preceded this open-label study was conducted at 167 centers worldwide, which are listed in the Final Study Report for that trial [1]. As of April 30, 2000 (the cut-off date for this interim report), 20 of these centers have *not* enrolled patients in this open-label continuation study. The investigators who have not participated in this follow-up study are:

[redacted]

6 INTRODUCTION

This trial is an open-label continuation of study 98-TOCR-007, which was a randomized, placebo-controlled, double-blind, multinational efficacy and safety trial to compare tolterodine [redacted] capsules and tolterodine immediate-release (IR) tablets with placebo in patients with overactive bladder [1].

Patients who fulfilled all eligibility criteria before randomization and completed the double-blind, 12-week treatment period in the initial trial were invited to participate in the open-label continuation trial (98-TOCR-007B). All patients who were eligible for the continuation trial were given tolterodine [redacted] capsules 4 mg qd without breaking the blind for the original trial. All patients retained the same number assigned in the blinded study.

The open-label continuation study has a treatment duration of 12-months and is designed to document the long-term safety and efficacy of the investigational product tolterodine [redacted] capsules. The Study Protocol is available in Appendix 2.

7 OBJECTIVES

The objective of this interim report is to present safety data on tolterodine [redacted] capsules 4 mg qd for two groups of patients who had the potential for 12 or 6 months treatment by April 30, 2000. The safety data comprise clinical safety assessments, i.e., the reporting of adverse events and withdrawals, and laboratory safety assessments.

8 METHODS

8.1 Overall Study Design

This is an open-label, uncontrolled, multicenter, multinational, non-randomized trial designed to document the long-term safety and efficacy of tolterodine [redacted] capsules. The trial is a continuation of the original protocol, 98-TOCR-007.

8.2 Data Quality Assurance

The new data from the 1072 patients included in this interim safety report have not been completely finalized but have been included in their available, existing state at the time of the interim cut-off date. Therefore, the database may be subject to minor changes and additions prior to final database closure. Data presented for the tolterodine [redacted] arm of study 007 are from the Final Study Report [1] of that study.

Pharmacia & Upjohn was responsible for independent quality assurance audits of the clinical trial processes at company sites worldwide. Audits of selected clinical investigator sites were also conducted to assess and help assure compliance with Good Clinical Practice and applicable regulatory requirements.

9 STUDY POPULATION, DEMOGRAPHICS AND EXTENT OF EXPOSURE

9.1 Study Population

To be included in the study, patients were required to fulfill the following inclusion and exclusion criteria.

9.1.1 Inclusion Criteria

1. Patients who fulfilled all eligibility criteria before randomization in the original protocol, 98-TOCR-007, and have completed the double-blind 12-week treatment period.
2. Patients able and willing to correctly complete the micturition charts.
3. Patients capable of understanding and having signed the informed consent form after full discussion of the research nature of the treatment and its risks and benefits.

9.1.2 Exclusion Criteria

1. Patients with poor compliance during the double-blind 12-week treatment period in the original protocol, 98-TOCR-007, i.e. Documented to have missed more than 25% of the prescribed trial medication (capsules and tablets), verified by the investigator.
2. Concurrent use of another investigational medication.
3. Patients on treatment with potent CYP3A4 inhibitors, such as macrolide antibiotics (erythromycin, clarithromycin) or antifungal agents (ketoconazole, itraconazole, miconazole), or expected to start such treatment during the trial.
4. Patients who have an ongoing serious adverse event from 98-TOCR-007.
5. Patients who are pregnant or nursing.
6. Female patients of childbearing potential not using reliable contraceptive methods during the entire trial period and for 1 month thereafter. Reliable contraceptive methods are intrauterine devices (IUD), contraceptive pills or combination type, hormonal implants and injectable contraceptives.

9.1.3 Criteria for Inclusion in the 12 month Population

A patient's eligibility for inclusion in the 12-month population for this interim report was based on whether or not the patient had the opportunity for 12 months exposure to tolterodine [redacted] 4 mg qd. For purposes of this report, 12 months tolterodine [redacted] treatment was defined as at least 351 days on treatment before the cut-off date of April 30, 2000. The duration of the wash-out period between study 007 and study 007B is included in the calculated extent of exposure.

This limitation resulted in the following rules:

- For patients randomized to tolterodine [redacted] in study 007 and who completed at least 9 months of treatment, the time in study 007B until the cut-off date (April 30, 2000) was added to that in study 007 for the total extent of exposure.
- For patients randomized to tolterodine [redacted] or placebo in study 007 and who commenced treatment with tolterodine [redacted] in study 007B prior to May 15, 1999, the total extent of exposure was identical to the time in the continuation study. No patient in this category commenced treatment before May 14, 1999.

Pharmacia & Upjohn c0026978

9.1.4 Criteria for Inclusion in the 6-month Population

A patient's eligibility for inclusion in the 6-month population for this interim report was based on whether or not the patient had the opportunity for 6 months exposure to tolterodine [redacted] 4 mg qd. For purposes of this report, 6 months tolterodine [redacted] treatment was defined as at least 169 days on treatment before the cut-off date of April 30, 2000. The duration of the wash-out period between study 007 and study 007B is included in the calculated extent of exposure.

This limitation resulted in the following rules:

- For patients randomized to tolterodine [redacted] in study 007 and who completed at least 3 months of treatment, the time in study 007B until the cut-off date (April 30, 2000) was added to that in study 007 for the total extent of exposure.
- For patients randomized to tolterodine [redacted] or placebo in study 007 and who commenced treatment with tolterodine [redacted] in study 007B prior to November 13, 1999, the total extent of exposure was identical to the time in the continuation study.

Of the patients enrolled in the trial as of 30 April, 2000, a total of 135 patients met the requirements for inclusion in the 12-month population and all 1072 patients in the 6-month population. The 1072 patients in this interim report included:

- 108 patients who completed 12 months of tolterodine [redacted] treatment;
- 27 patients who were prematurely withdrawn from 12 months treatment;
- 941 patients who completed at least 6 months of tolterodine [redacted] treatment;
- 131 patients who were prematurely withdrawn from 6 months treatment; and
- No patient had less than 6 months treatment.

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ON ORIGINAL

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9.2 Demographics

Summaries of the demographic data for the 12-month and the 6-month populations are presented in Table 1.
A comparison with that of the tolterodine [redacted] treatment arm of study 007 shows that these populations are similar.

Table 1. Patient Demographics, 12-month and 6-month Populations and Tolterodine [redacted] Treatment Arm of Study 007

Demographic	98-TOCR-007B 12-month Population[1] (n = 135)	98-TOCR- 007B 6-month Population[2] (n = 1072)	98-TOCR-007 Tolterodine [redacted] Treatment Arm[3] (n=507)
Sex [n (%)]			
Male	19 (14.1)	191 (17.8)	90 (17.8)
Female	116 (85.9)	881 (82.2)	417 (82.2)
Race [n (%)]			
White	129 (95.6)	1026 (95.7)	483 (95.3)
Black	5 (3.7)	32 (3.0)	17 (3.4)
Asian or Pacific Islander	1 (0.7)	7 (0.7)	5 (1.0)
Mixed	—	7 (0.7)	1 (0.2)
Not allowed to ask	—	—	1 (0.2)
Age (years)			
Mean (SD)	59.7 (14.4)	60.3 (13.7)	60.3 (14.4)
Range	19.6 to 89.4	19.6 to 93.2	19.6 to 89.4
n	135	1072	506

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 12 months prior to April 30, 2000.

[2] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 6 months prior to April 30, 2000.

[3] All patients in the tolterodine [redacted] treatment arm of study 007 were included (ITT population).

9.3 Extent of Exposure to Tolterodine [redacted]

Table 2 summarizes the extent of exposure to tolterodine [redacted] in the 12-month population. Based on 135 patients the total time of exposure to tolterodine [redacted] in this population was >120 patient-years. Table 3 summarizes the extent of exposure to tolterodine [redacted] in the 6-month population. Based on 1072 patients, the total time of exposure to tolterodine [redacted] in this population was >700 patient years.

Pharmacia & Upjohn c0026978

Table 2. Duration of Tolterodine — Treatment, 12-month Population[1]

Duration of Treatment	No. of Patients (n = 135)
0 to <1 month	135
1 to <2 months	135
2 to <3 months	135
3 to <4 months	135
4 to <5 months	133
5 to <6 months	130
6 to <7 months	126
7 to <8 months	118
8 to <9 months	113
9 to <10 months	112
10 to <11 months	109
11 to <12 months	108
≥12 months	108

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine — for 12 months prior to April 30, 2000.

Table 3. Duration of Tolterodine — Treatment, 6-month Population[1]

Duration of Treatment	No. of Patients (n = 1072)
0 to <1 month	1072
1 to <2 months	1060
2 to <3 months	1043
3 to <4 months	1018
4 to <5 months	974
5 to <6 months	954
≥6 months	941

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine — for 6 months prior to April 30, 2000.

10 SAFETY VARIABLES

10.1 Laboratory Safety Variables

All observed changes in clinical chemistry and hematology variables of clinical relevance are continuously reported as adverse events and are included in this report. All laboratory assessments performed in the open-label follow-up study will be evaluated in the final study report for study 007B.

Changes in laboratory variables were reported as adverse events for 3 patients in the 12-month population, which are listed in Table 4, and for 23 patients in the 6-month population, which are listed in Table 5.

Table 4. Change in Laboratory Variables Reported as Adverse Events, 12-month Population

Adverse Event		12-month Population[1] (n = 135)		
Body System	Preferred Term	Patient No.	Seriousness	Severity
Liver & Biliary	Hepatic enzymes incr	3049	No	Moderate
Metabolic & Nutr	Phosphatase alkaline incr	1154	No	Mild
	Phosphatase alkaline incr	1402	No	Mild

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 12 months prior to April 30, 2000.

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ON ORIGINAL

Table 5. Change in Laboratory Variables Reported as Adverse Events, 6-month Population

Adverse Event		6-month Population[1] (n = 1072)		
Body System	Preferred Term	Patient No.	Seriousness	Severity
Liver & Biliary	Hepatic enzymes incr	1512	No	Mild
Metabolic & Nutr	Diabetes mellitus	1027	No	Mild
	Diabetes mellitus	1056	No	Mild
	Diabetes mellitus	1867	No	Mild
	Diabetes mellitus	2771	No	Moderate
	Hypercholesterolaemia	1687	No	Mild
	Hypercholesterolaemia	1757	No	Mild
	Hypercholesterolaemia	2989	No	Moderate
	Hyperglycemia	1784	No	Moderate
	Hyperglycemia	2839	No	Mild
	Hyperkalaemia	1687	No	Moderate
	Hyperuricaemia	3053	No	Mild
	Hypoglycemia	2397	No	Severe
Endocrine	Elevated TSH	1333	No	Mild
	Elevated TSH	1628	No	Mild
	Hyperthyroidism	2398	No	Moderate
	Hypothyroidism	1804	No	Mild
	Hypothyroidism	2376	No	Moderate
Red blood cell	Anemia	2057	No	Mild
	Anemia	2635	No	Mild
	Anemia hemolytic	1493	Yes	Severe
Platelet/Bleed	Thrombocytopenia	3052	No	Mild
General	Dev Lab Value (Hemocult)	1336	No	Mild

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine for 6 months prior to April 30, 2000.

10.2 Adverse Events

Dry mouth, constipation, and headache were the 3 most commonly reported events (>5%) in the 12-month and the 6-month populations, and among patients treated with tolterodine in the blinded study (007). The slight increases in the 12-month population in the reporting of xerophthalmia (dry eyes), fatigue, upper respiratory tract infection, urinary tract infection, is natural, except for dry eyes, since the incidence of common and recurrent diseases such as infections increases with a longer observation period, apart from the seasonal differences.

Pharmacia & Upjohn c0026978

All patients reporting adverse events in the 12-month and 6-month populations and in the tolterodine [redacted] treatment arm of study 007 are given in Table 6.

Table 6. Number of Patients Reporting Adverse Events by Body System and Preferred Term (WHO preferred term ≥ 1%), 12-month and 6-month Populations and Tolterodine PR Treatment Arm of Study 007

		12-months population[1]		6-months population[2]		98-TOCR-007 (Tolterodine [redacted]	
Adverse Event		n=135		n=1072		n=505	
Body system	Preferred term	n	(%)	n	(%)	n	(%)
Skin & Append.	Rash	5	(3.7)	11	(1.0)	4	(0.8)
Musculo-Skel.	Arthritis	4	(3.0)	13	(1.2)	1	(0.2)
Cent & Per Nerv	Dizziness	4	(3.0)	21	(2.0)	11	(2.2)
Autonomic Nerv	Mouth dry	39	(28.9)	203	(18.9)	118	(23.4)
Vision	Vision abnormal	3	(2.2)	10	(0.9)	6	(1.2)
	Xerophthalmia	9	(6.7)	25	(2.3)	17	(3.4)
Psychiatric	Depression	1	(0.7)	15	(1.4)	3	(0.6)
	Insomnia	2	(1.5)	9	(0.8)	7	(1.4)
	Somnolence	4	(3.0)	18	(1.7)	14	(2.8)
Gastro-Intest	Abdominal pain	4	(3.0)	31	(2.9)	19	(3.8)
	Constipation	14	(10.4)	60	(5.6)	30	(5.9)
	Diarrhoea	2	(1.5)	14	(1.3)	10	(2.0)
	Dyspepsia	6	(4.4)	28	(2.6)	15	(3.0)
	Flatulence	4	(3.0)	15	(1.4)	10	(2.0)
	Nausea	3	(2.2)	17	(1.6)	7	(1.4)
Metabolic & Nut	Weight increase	1	(0.7)	14	(1.3)	3	(0.6)
Cardiovascular	Hypertension	3	(2.2)	17	(1.6)	7	(1.4)
Respiratory	Bronchitis	3	(2.2)	26	(2.4)	2	(0.4)
	Coughing	7	(5.2)	12	(1.1)	4	(0.8)
	Sinusitis	5	(3.7)	25	(2.3)	9	(1.8)
	Upper resp tract infection	13	(9.6)	47	(4.4)	14	(2.8)
Urinary	Cystitis	3	(2.2)	20	(1.9)	4	(0.8)
	Dysuria	4	(3.0)	12	(1.1)	5	(1.0)
	Urinary tract infection	8	(5.9)	55	(5.1)	16	(3.2)
General	Back pain	5	(3.7)	31	(2.9)	4	(0.8)
	Chest pain	3	(2.2)	14	(1.3)	4	(0.8)
	Fatigue	7	(5.2)	21	(2.0)	11	(2.2)
	Headache	10	(7.4)	46	(4.3)	32	(6.3)
	Influenza-like symptoms	6	(4.4)	39	(3.6)	4	(0.8)
	Oedema peripheral	2	(1.5)	9	(0.8)	7	(1.4)
	Pain	1	(0.7)	19	(1.8)	6	(1.2)

		12-months population[3]		6-months population[2]		98-TOCR-007 (Tolterodine [redacted]	
General	Surgical intervention	1	(0.7)	16	(1.5)	6	(1.2)
Resistance Mech	Infection	5	(3.7)	15	(1.4)	4	(0.8)

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 12 months prior to December 31, 1999.

[2] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] or 6 months prior to December 31, 1999.

[3] Two patients in the tolterodine [redacted] reatment arm of study 007 did not receive study medication and were excluded from the safety population.

Note: The incidence of adverse events in the 12-month and 6-month populations includes some occurrences of adverse events that are also reported in study 007.

10.2.1 Drug-related Adverse Events

In general, assessments of causality of adverse events were similar between the open-label (007B) and the blinded study (007).

In the 12-month population, the most commonly reported (WHO preferred term >1%) adverse events assessed by the investigator as possibly related to study treatment were dry mouth (24.4%), constipation (5.9%), xerophthalmia (4.4%), headache (3.7%), dyspepsia (2.2%), nausea (2.2%), fatigue (2.2%), dizziness (1.5%), diarrhoea (1.5%), and flatulence (1.5%).

In the 6-month population, the most commonly reported adverse events assessed by the investigator as possibly related to study treatment were dry mouth (13.4%), constipation (3.2%), xerophthalmia (2.0%), headache (1.6%), and dyspepsia (1.2%).

In the tolterodine [redacted] treatment arm of study 007 the most commonly reported adverse events were dry mouth (22.2%), constipation (5.2%), headache (4.0%), xerophthalmia (2.8%), and dyspepsia (2.0%) followed by flatulence (1.4%), fatigue (1.4%), somnolence (1.2%), diarrhoea (1.2%), nausea (1.2%), and dizziness (1.0%).

All adverse events in both the 12-month, and 6-month populations and in the tolterodine [redacted] treatment arm of study 007 that were regarded by the investigator as possibly drug related are given in Appendix 3.

10.3 Withdrawals

The analysis of premature withdrawals was based on preliminary data. The incidence of withdrawals due to adverse events in the 12-month and 6-month populations was similar to the tolterodine [redacted] treatment arm of study 007. The total number of withdrawals was greater, but the relative withdrawal rate in relation to the length of exposure was similar. Table 7 shows the number of patients prematurely withdrawn from treatment as of April 30, 2000.

Table 7. Number of Patients Prematurely Withdrawn from Tolterodine [redacted] Treatment as of April 30, 2000; 12-month and 6-month Populations and Tolterodine [redacted] Treatment Arm of Study 007

Reason for Withdrawal	98-TOCR-007B 12-month Popuplation[1] (n = 135)		98-TOCR-007B 6-month Population[2] (n = 1072)		98-TOCR-007 Tolterodine [redacted] Treatment Arm[3] (n = 505)	
	n	(%)	n	(%)	n	(%)
Adverse event	14	(10.4)	77	(7.2)	27	(5.3)
Protocol violation	1	(0.7)	11	(1.0)	10	(2.0)
Consent withdrawn	2	(1.5)	37	(3.5)	6	(1.2)
Lost to follow-up	—	—	7	(0.7)	6	(1.2)
Lack of efficacy	13	(9.6)	78	(7.3)	6	(1.2)
Total withdrawn	30[4]	(22.2)	210[5]	(19.6)	55	(10.9)

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 12 months prior to April 30, 2000.

[2] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] for 6 months prior to April 30, 2000.

[3] Two patients in the tolterodine [redacted] treatment arm, study 007, did not receive study medication and were excluded from the safety population.

[4] Patients withdrawn *after* 12 months of treatment are included.

[5] Patients withdrawn *after* 6 months of treatment are included.

Of the 13 patients in the 12-month population reporting adverse event leading to premature withdrawal from treatment, headache was reported by 3 patients (1267, 2 events, 1373, 2003), dizziness by 3 patients (1402, 1675, 2003). Two patients reported dry mouth (1402, 3029). Each of the following events was reported only by one patient, abdominal pain (1340), asthenia (1402), constipation (1373), hepatic enzymes increased (3049), infection (1025), micturition frequency (1402), micturition urgency (1406, 2 events), nausea (1675), rhinitis (1373), sudden death (1161), urinary tract infection (1387), weight increase (2773), and xerophthalmia (3029).

Of the 74 patients in the 6-month population reporting adverse event leading to premature withdrawal from treatment, the most frequently reported were dry mouth (20 patients), headache (7 patients), abdominal pain (6 patients), dizziness (6 patients), and fatigue (5 patients), and constipation (5 patients).

Of the 27 patients in the tolterodine PR arm, study 007, the most frequently reported adverse events leading to premature withdrawal from treatment, were dry mouth (8 patients), constipation (5 patients), and headache (4 patients).

A table including all adverse events leading to premature withdrawal is given in Appendix 4.

10.4 Serious Adverse Events

Table 8 lists all serious adverse events that occurred in the 12-month and 6-month populations as of April 30, 2000 and in the tolterodine treatment arm of study 007. In both populations, all serious adverse events were regarded by the investigator as unrelated to study drug, except for three events not yet assessed.

Narratives for all patients in study 007B with serious adverse events reported as of April 30, 2000 are included in Appendix 5, by population. Narratives for patients reporting serious adverse events in study 007 are available in the final study report [1].

Table 8. Serious Adverse Events Reported for the 12-month and 6-month Populations and the Tolterodine [redacted] Treatment Arm of Study 007

Adverse Event		12 months population[1]	6 months population[2]	98-TOCR-007 (Tolterodine)
Body system	Preferred term	n=135	n=1072	n=505
Skin & Append.	Rash erythematous	1	1	
Musculo-Skel.	Arthritis		1	
	Arthropathy		1	
	Fracture		2	
	Myopathy		1	
	Tendon disorder		1	
Cent & Per Nerv	Ms aggravated		1	
Autonomic Nerv	Palpitation			1
Gastro-Intest	Appendicitis		1	
	Diverticulitis		1	1
	Faecal incontinence		1	
	Gastroesophageal reflux		1	
	Hernia nos		1	1
	Intestinal obstruction			1
	Intestinal perforation		1	
	Surgical intervention		2	

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Adverse Event		12 months population[1]	6 months population[2]	98-TOCR-007 (Tolterodine [redacted]
Liver & Biliary	Cholecystitis		1	
Cardiovascular	Aneurysm		1	
	Cardiac failure		3	
Myo/Endo/Peri	Angina pectoris		1	
	Angina pectoris aggravated		1	
	Myocardial infarction		1	
	Myocardial ischaemia		1	
Heart R & R	Fibrillation atrial		1	
Extracardiac	Cerebrovascular disorder		1	
	Thrombophlebitis		1	
	Thrombosis arterial leg		1	
	Vascular disorder		1	
Respiratory	Dyspnoea	1	2	
	Pneumonia		4	
	Pulmonary oedema		1	
	Respiratory insufficiency		1	
	Sinusitis		1	
Red blood cell	Anaemia haemolytic		1	
Platelet/Bleed	Thrombosis	1	2	
Urinary	Albuminuria		1	
	Urinary tract infection	1	2	
Reproductive-F	Endometrial disorder		1	
	Endometriosis		1	
	Pregnancy unintended		2	
	Uterovaginal prolapse		1	
Neoplasms	Breast neoplasm malignant female	1	3	1
	Pulmonary carcinoma		1	

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Adverse Event		12 months population[1]	6 months population[2]	98-TOCR-007 (Tolterodine [redacted]
General	Allergic reaction		1	
	Chest pain		4	1
	Myocarditis		1	
	Sudden death	1	1	1
	Surgical intervention		4	1
Resistance Mech	Infection	1	2	1
Events	Fall		2	
	Food poisoning		1	
	Inflicted injury		1	
Total events		7	71	9

[1] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] or 12 months prior to April 30, 2000.

[2] Patients who took study medication in study 007B and had the opportunity to take tolterodine [redacted] or 6 months prior to April 30, 2000.

[3] Two patients in the tolterodine [redacted] treatment arm of study 007 did not receive study medication and were excluded from the safety population.

Note: The incidence of adverse events in the 12-month and 6-month populations includes some occurrences of adverse events that are also reported in study 007.

10.4.1 Exposure in Utero

Two patients (1844, 3030) were withdrawn from treatment after pregnancy was reported. These patients will be closely monitored until the offspring is born or the pregnancy is otherwise terminated. The narratives for these patients are included with the narratives for serious adverse events in Appendix 5.

10.5 Deaths

Two deaths has been reported in study 98-TOCR-007B as of April 30, 2000, one in the 12-month population (1161) and one in the 6-month population (3099). The narratives are provided below and in Appendix 5.

Subject 1161/Center 203 US. *Sudden death*

A 70-year-old female was found dead at home of a possible heart attack after 263 days on study treatment (days in blinded study included). Medical history: allergy (codeine), hypertension, hypothyroidism, arthritis, hiatus hernia, angiomyolipoma and depression. Concomitant medication: methyltestosterone, alprozalam, losartan, levothyroxine, omeprazole, acetylsalicylic acid, multivitamins, citalopram hydrobromide, hydrochlorothiazide, nicotine, Arthrotec® and celecoxib. The investigator considered the adverse event to be unrelated to study treatment. The subject was randomized to tolterodine PR 4 mg qd in study 98-TOCR-007

Subject 3099/Center 030 BE. *Inflicted injury*

This 43-year-old female died from the complications of strangulation by husband after 44 days of study treatment. The subject was previously treated with tolterodine [redacted] 2 mg bid for 3 months in study 98-TOCR-007. The investigator considered the adverse event to be unrelated to study treatment.

11 SAFETY CONCLUSIONS

No new safety concerns were identified in the cohort of 135 patients treated for 12 months or of the 1072 patients treated for 6 months with tolterodine [redacted] capsules 4 mg qd from the incidences of adverse events, serious adverse events, premature withdrawals or adverse events resulting in withdrawals. The overall number and type of adverse events reported for the 12-month and 6-month populations were similar to those reported for tolterodine [redacted] treated patients in the controlled study (98-TOCR-007).

12 REFERENCE LIST

1. Söderström J-P, Szamosi J. Clinical efficacy and tolerability/safety of tolterodine [redacted] release capsules and tolterodine immediate release tablets vs placebo. A randomized, double-blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder. Final Study Report on 98-TOCR-007. Pharmacia & Upjohn Document No. c0013194.

Pharmacia & Upjohn

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

May 17, 2000

DUPLICATE

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

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

General Correspondence

NEW CORRESP
NC

Dear Sir/Madam:

Attached please find a letter from International Processing Corporation (third party manufacturer) to the Cincinnati District Office of the Food and Drug Administration.

It has been IPC's previous experience to confer with the District on matters such as Process Validation and as such they have written the enclosed letter.

It is our intention by forwarding a copy to the Division and ultimately to the review chemist, that he be aware of this communication and correspond with the District as he deems necessary regarding the contents of the letter.

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:kmv
Attachments

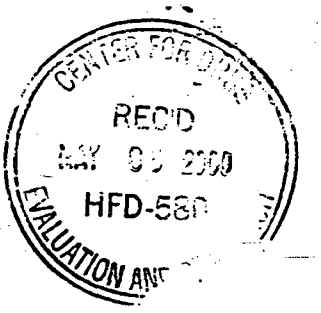
cc: Lana Pauls HFD-580

Pharmacia & Upjohn

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

May 4, 2000

DUPLICATE



Dr. Roy Blay
Office of Medical Policy, DSI, GCP Branch 1
HFD-46
7520 Standish Place
Rockville, MD 20855

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

General Correspondence
Requested Site Information

NC

Dear Dr. Blay:

In response to your April 27 request, I have consulted with my clinical colleagues and been informed that the site information provided to you on April 10, 2000 for a similar request for NDA 20-771/S-004 would be the same information for NDA 21-228. Therefore, as we have agreed, this information will not be supplied a second time. The information provided on April 10 may be used for the NDA 21-228 inspections as well.

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:lmf

cc: Division of Division of Reproductive Health and Urologic Drug Products HFD-580

Pharmacia&Upjohn

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

May 1, 2000

Ms. Evelyn Farinas
Division of Reproductive Health and Urologic Drug Products, HFD-580
Room-17B-45
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

Desk Copy

Dear Evelyn:

In response to your request, enclosed please find a WORD version of the proposed package insert submitted with the above NDA.

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

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

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

GGS/crdt

Enclosure

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 — 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

Pharmacia & Upjohn

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

ORIGINAL

April 3, 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

See Chemistry Review #1
/S/
12-APR-2000

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

Amendment #2 ORIG AMENDMENT

4/13/00

BC

Dear Sir/Madam:

Attached please find the manufacturing site information requested by Evelyn Farinas on March 27, 2000. The attached list includes all facility information related to the above NDA. All sites are PAI ready.

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

4/13/00
Received
NAI
BSO

REVIEWS COMPLETED
CONCURRENCE
☐ LETTER ☐ N.A.I. ☐ MEMO
GGS 4-14-00
CSO INITIALS DATE

NDA 21-228

Tolterodine [redacted] Release Capsules

Field Copy Statement

In accord with CFR §314.70(a), this is to certify that a field copy of this Chemistry, Manufacturing and Controls Amendment to NDA 21-228 dated April 3, 2000 has been provided to the Detroit District Office.

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:kmv

APPEARS THIS WAY
ON ORIGINAL

PHARMACIA & UPJOHN, INC. FACSIMILE

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

TO: Evelyn Farinas DATE: April 3, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA 21-228

FROM: Gregory Shawaryn
PHONE: 616-833-8239

TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 2

Message:

Dear Evelyn,

Attached please find the manufacturing site information you requested on March 27, 2000. The attached list includes all facility information related to the above NDA.

All sites are PAI ready.

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