

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-228 S006

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



10/8/03

Food and Drug Administration
Rockville, MD 20857NDA 20-771
NDA 21-228Pharmacia & Upjohn Company
Attention: Gregory G. Shawaryn
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Reference is made to your correspondence dated September 29, 2003 requesting a change to FDA's January 23, 2001, Written Request for pediatric studies for tolterodine tartrate tablets.

We have reviewed your proposed change and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on January 23, 2001 and amended on November 15, 2001, August 5, 2002, and March 3, 2003 remain the same.

Study #3. Drug Information:

We agree with your request to change this section to reflect doses employed in protocol 583-URO-0581-003.

Therefore, we are amending the sentence that currently reads as follows:

"The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 2 mg/day for 4 weeks, 4 mg/kg/day for four weeks, and 6 mg/kg/day for four weeks."

to:

"The total daily dose for each patient will be administered orally **once a day** and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 2 mg/day for four weeks, **4 mg/day** for four weeks, and **6 mg/day** for four weeks."

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter and the amendment dated November 15, 2001 and the amendment dated August 5, 2002 must be submitted to the Agency on or before October 15, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a **supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY**"

NDA 20-771

NDA 21-228

Page 2

DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Jean King, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.

/s/

Julie Beitz
10/8/03 06:09:52 PM

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8/15/02



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857NDA 20-771
NDA 21-228Pharmacia & Upjohn Company
Attention: Gregory G. Shawaryn
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Reference is made to your correspondence dated April 9, 2002, June 14, 2002, and July 15, 2002 requesting changes to FDA's January 23, 2001, Written Request for pediatric studies for tolterodine tartrate tablets.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on January 23, 2001 and amended on November 15, 2001 remain the same.

Study #1, Drug Information:

We agree with your request to change this section to correlate to doses employed in Protocol 583E-URO-0581-001.

Therefore, we are amending the sentence that currently reads as follows:

"The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.2-2.0 mg that will be administered orally in divided doses."

to

"The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks."

Study #1, Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #2, Drug Information:

We agree with your request to change the section to correlate to doses employed in Protocol 583E-URO-0581-002.

Therefore, we are amending the sentence that currently reads as follows:

"The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.5-4 mg that will be administered orally in divided doses."

to

"The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 0.03 mg/kg/day for 4 weeks, 0.06 mg/kg/day for four weeks, and 0.12 mg/kg/day for four weeks."

Study #2, Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #3, Drug Information:

We agree with your request to change the section to correlate to doses employed in Protocol 583E-URO-0581-003.

Therefore, we are amending the sentence that currently reads as follows:

"The patient's clinician will select the appropriate total daily dose for each patient within the range of 2-4 mg. The dose will be administered orally once daily."

to

"The total daily dose for each patient will be administered orally in divided doses and will follow a sequential dose escalation design, with each patient serving as his/her own control, increasing through three dosage levels: 2 mg/day for 4 weeks, 4 mg/kg/day for four weeks, and 6 mg/kg/day for four weeks."

Study #3. Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Study #4. Timeframe for submitting reports of the study:

We agree with your request to change the timeframe for submitting reports of this study by three months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before December 15, 2002."

to:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter and the amendment dated November 15, 2001 must be submitted to the Agency on or before March 15, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting

the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Jen Mercier, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Victor Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Victor Raczkowski
8/5/02 10:25:38 AM

7/3/02

Amendment



CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-771
NDA 21-228

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

Dear Mr. Shawaryn:

Please refer to the Written Request, originally issued January 23, 2001, that you received from the Center for Drug Evaluation and Research. This Written Request was issued under Section 505A of the Federal Food, Drug, and Cosmetic Act to conduct pediatric studies using tolterodine. As you know, on January 4, 2002, the President signed into law the "Best Pharmaceuticals for Children Act," (BPCA) which both extended the pediatric exclusivity program established in the 1997 FDA Modernization Act (FDAMA) and provided new mechanisms for studying pediatric uses for drugs. The BPCA also contains new provisions of which you should be aware related to user fees, priority review, drug labeling, and disclosure of pediatric study results. FDA is revising its Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act to provide additional information on the pediatric drugs study provisions of the BPCA.

FDA has received questions about whether sponsors who were issued Written Requests to conduct pediatric studies prior to passage of the BPCA, but who had not as yet submitted the reports of the studies as of January 4, 2002, would be governed by the provisions of FDAMA or the BPCA. In order to maximize the benefit to be derived from the BPCA and to minimize uncertainty and delay in implementing the pediatric exclusivity program, FDA has decided to reissue those Written Requests originally issued prior to passage of the BPCA for which studies have not already been submitted.

This letter is your notification that the Written Request (and any subsequent amendments) described above is considered to be reissued as of the date of this letter. The terms of the Written Request are not otherwise altered by this letter. If you believe that the Written Request should be amended, please contact the division directly.

Please note that if the original Written Request was issued under Section 505A(a), it will now be considered to be issued under Section 505A(b), due to the reordering of the sections, as described in Section 19 of the BPCA. If the original Written Request was issued under Section 505A(c), it will still be considered to be issued under Section 505A(c).

An important change to note is that, if the drug for which FDA issued the Written Request under 505A(c) has listed patent or exclusivity protection, new section 505(d)(4)(A) states that within 180 days of receipt of this "reissued" Written Request, you must notify FDA when the pediatric studies will be initiated, or that you do not agree to conduct the requested studies. New provisions at Section 505(d)(4)(B)-(F) describe alternative methods for obtaining these pediatric studies.

If you have questions regarding the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. As noted above, requests to amend your Written Request should be directed to the review division.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug
Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
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Amendment



NDA 20-771

NDA 21-228

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

Dear Mr. Shawaryn:

Reference is made to your correspondence dated September 10, 2002 and December 20, 2002 requesting changes to FDA's January 23, 2001, Written Request for pediatric studies for tolterodine tartrate tablets.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on January 23, 2001 and amended on November 15, 2001 and amended on August 5, 2002 remain the same.

Study #1, Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by seven months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

to:

"A report of the above study must be submitted to the Agency on or before October 15, 2003."

Study #2, Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by seven months.

Therefore, we are amending the sentence that currently reads as follows:

"A report of the above study must be submitted to the Agency on or before March 15, 2003."

to:

“A report of the above study must be submitted to the Agency on or before October 15, 2003.”

Study #3. Timeframe for submitting reports of the study:

We agree to extend the timeframe for submitting a report of this study by seven months.

Therefore, we are amending the sentence that currently reads as follows:

“A report of the above study must be submitted to the Agency on or before March 15, 2003.”

to:

“A report of the above study must be submitted to the Agency on or before October 15, 2003.”

Study #4. Timeframe for submitting reports of the study:

We agree with your request to change the timeframe for submitting reports of this study by seven months.

Therefore, we are amending the sentence that currently reads as follows:

“A report of the above study must be submitted to the Agency on or before March 15, 2003.”

to:

“A report of the above study must be submitted to the Agency on or before October 15, 2003.”

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter and the amendment dated November 15, 2001 and the amendment dated August 5, 2002 must be submitted to the Agency on or before October 15, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter and the amendment dated November 15, 2001 and the amendment dated August 5, 2002 must be submitted to the Agency on or before October 15, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOGOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Jean King, Regulatory Project Manager, at 301-827-4260.

Sincerely,

Florence Houn, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Florence Houn
3/3/03 07:20:10 AM

11/15/01

Amendment



NDA 20-771
NDA 21-228

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

Dear Mr. Shawaryn:

Reference is made to your correspondence dated August 20, 2001, requesting changes to FDA's January 23, 2001, Written Request for pediatric studies for tolterodine tartrate tablets.

We have reviewed your proposed changes and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on January 23, 2001, remain the same.

Study #4. Number of Patients to be studied:

We are in agreement that there is a typographical error relative to the formulation to be used in Study #4 of your Written Request in the sentence under the heading "Number of patients to be studied."

Therefore, we are amending the sentence that currently read as follows:

"Enroll approximately 300 patients, with approximately equal number of patients in the five-seven year old age group and in the eight-ten year old age group, to ensure a minimum of 100 patients completing 24 weeks of treatment with Detrol (tolterodine tartrate) syrup or tablets."

to

"Enroll approximately 300 patients, with approximately equal number of patients in the five-seven year old age group and in the eight-ten year old age group, to ensure a minimum of 100 patients completing 24 weeks of treatment with tolterodine extended release capsules"

Reports of the studies that meet the terms of the Written Request dated January 23, 2001, as amended by this letter must be submitted to the Agency on or before December 15, 2002, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC

NDA 20-771

NDA 21-228

Page 2

STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED” in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked “PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES” in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

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

Sincerely,

{ See appended electronic signature page }

Victor Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.

/s/

Victor Raczkowski
11/15/01 09:02:48 AM

Original Written Request

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1/23/01



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-771
NDA 21-228

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

Dear Mr. Shawaryn:

Reference is made to your Proposed Pediatric Study Request submitted on June 28, 2000 for tolterodine tartrate extended release capsules to NDA 21-228.

To obtain needed pediatric information on tolterodine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following four studies and two critical analyses:

Study #1:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), and safety study

Objectives:

1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of Detrol® (tolterodine tartrate) syrup to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine.
2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.
3. To evaluate the effect and safety of Detrol® (tolterodine tartrate) syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

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JAN 30 2001

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of two weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages one month to four years

Number of patients to be studied:

Enroll a sufficient number of patients to adequately characterize the PK/PD parameters. PK/PD parameters must be obtained on a minimum of eight patients, with at least three of these patients being less than 6 months of age.

Study endpoints:

1. PK: appropriate analysis of tolterodine and DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group.
2. PD: appropriate urodynamic evaluation. Evaluation may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions.
3. Dose-response: characterization of dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
4. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters
5. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is tolterodine syrup. It is currently not a commercially available formulation. The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.2-2 mg that will be administered orally in divided doses.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max} , and C_{min} for tolterodine and DD 01.
2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment.

Written Request

3. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #2:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), and safety study

Objectives:

1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of tolterodine tartrate syrup to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine.
2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.
3. To evaluate the effect and safety of tolterodine tartrate syrup in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of two weeks of treatment with tolterodine.

Age group in which study will be performed:

Written Request

Ages five to ten years

Number of patients to be studied:

Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.

Study endpoints:

1. PK: appropriate analysis of tolterodine and DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group
2. PD: appropriate urodynamic evaluation. Evaluations may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions.
3. Dose-response: dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinence episodes per day
5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters
6. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following currently commercially not available formulation: tolterodine syrup. The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.5–4 mg that will be administered orally in divided doses.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max} , and C_{min} for tolterodine and DD 01.
2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment.
3. Diary: number of micturitions per 24 hours and number of incontinence episodes per day (diary data) to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
4. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.

Written Request

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #3:

Type of study:

Pharmacokinetic (PK), pharmacodynamic (PD [urodynamic]), and safety study

Objectives:

1. To evaluate the pharmacokinetics of tolterodine and its metabolite (DD01) following administration of tolterodine tartrate extended release capsules to pediatric patients with detrusor hyperreflexia due to neurogenic conditions who are on stable divided daily doses of tolterodine.
2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.
3. To evaluate the effect and safety of tolterodine tartrate extended release capsules in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple dose-level, open label, minimum 2-week duration, PK, PD, and safety study.

For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 day washout period off medication. Urodynamic evaluation will be repeated after a minimum of two weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages eleven to fifteen years

Number of patients to be studied:

Written Request

Enroll approximately 15 patients to have a minimum of eight patients for describing the PK/PD profile.

Study endpoints:

1. PK: appropriate analysis of tolterodine and DD 01 metabolite plasma concentration-time profiles; the sampling should be adequate to characterize the complete PK profile in this age group
2. PD: appropriate urodynamic evaluation. Evaluations may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions.
3. Dose-response: characterization of dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
4. Clinical: diary data to include number of micturitions per 24 hours and number of incontinence episodes per day
5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular (including electrocardiograms) and laboratory parameters
6. Safety: number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following commercially not yet available formulation: tolterodine extended release capsules. The patient's clinician will select the appropriate total daily dose for each patient within the range of 2–4 mg. The dose will be administered orally once daily.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: descriptive analysis to include reporting of AUC, C_{max} , and C_{min} for tolterodine and DD 01.
2. PD: urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment.
3. Diary: number of micturitions per 24 hours and number of incontinence episodes per day (diary data) to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
4. Safety: safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Written Request

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #4:

Type of study:

Clinical efficacy, PK, and safety study in patients with overactive bladder

Objectives:

1. To compare the *clinical* efficacy (as assessed by the number of incontinence episodes) of tolterodine extended release and placebo.
2. To document the safety and tolerability of tolterodine extended release capsules in pediatric patients with overactive bladder.
3. To evaluate the population PK of tolterodine and its metabolite (DD01) following administration of tolterodine extended release capsules using sparse sampling technique.
4. To evaluate dose-effect (diary data) and concentration-effect (diary data) in order to establish one or more safe and effective dosage regimens in pediatric patients with overactive bladder.

Indication:

Overactive bladder

Study design:

Minimum 12-week, double blind, two parallel group, placebo controlled, two-to-one (test drug/placebo) randomized, clinical efficacy and safety study followed by a minimum 12-week, safety extension study.

Age group in which study will be performed:

Ages five to ten years

Number of patients to be studied:

Enroll approximately 300 patients, with approximately equal number of patients in the five-seven year old age group and in the eight-ten year old age group, to ensure a minimum of 100 patients completing 24 weeks of treatment with Detrol® (tolterodine tartrate) syrup or tablets.

Study endpoints:

Written Request

1. *Primary endpoint*: change from baseline in number of incontinence episodes per week after 12 weeks of treatment. *Other endpoints*: the change from baseline in mean number of micturitions per 24 hours after 12 weeks of treatment, the change from baseline in mean urinary volume voided per micturition after 12 weeks of treatment, and appropriate population pharmacokinetic analysis of tolterodine and DD 01 metabolite data.
2. Dose-response: characterization of dose(in mg per kg)-effect (diary data) and concentration-effect (diary data)
3. Safety: incidence and severity of adverse events, postvoid residual urine, cardiovascular (including electrocardiograms) and laboratory abnormalities
4. Safety: number of patients terminated prematurely from the trial

Drug information:

The drug product to be used in this study is the following formulations: tolterodine extended release capsules, 2 mg, administered orally once a day in the morning.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of *anticholinergic agents* (e.g. constipation, dry mouth).

Statistical information:

1. All statistical tests will be two-sided and the level of significance will be 0.05.
2. PK: appropriate population PK analysis for drug and DD01 metabolite.
3. Micturition Diary Data: diary data are to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with measurements on treatment.
4. Safety: safety measurements are to be tabulated by treatment group, body system and preferred term for both 12 week efficacy and 12 week safety extension trials. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data. Patients with abnormal postvoid residual urine findings, serious adverse events, or who withdraw due to an adverse event will be reported on a case-by-case basis.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

A report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent

Written Request

protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Critical Analyses:

1. Provide a critical analysis of urodynamic data in adults with overactive bladder treated with tolterodine and perform a subset analysis of this data in adults with detrusor hyperreflexia. This will be submitted with the final study reports. The analysis will review clinical trial data and the published literature and will describe the dose-effect (urodynamic) of tolterodine in this population.
2. Provide a critical analysis of tolterodine safety in pediatric patients including data from clinical trials and published literature. This will be submitted with the final study reports.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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

Sincerely,

Victor Raczowski, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Victor Raczkowski
1/23/01 09:34:25 AM



NDA 21-228/S 006
NDA 20-771/000 C

NDA 21-228

Pfizer Inc.
Attention: Tara Feehan
Manager, US Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Feehan:

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

Name of Drug Product:	Detrol LA (tolterodine tartrate extended release capsules)
NDA Number:	NDA 21-228/NDA 20-771 (correspondence only)
Supplement number:	006
Review Priority Classification:	Priority (P)
Date of supplement:	October 10, 2003
Date of receipt:	October 14, 2003

This supplemental application contains pediatric study reports, a request for pediatric exclusivity determination, and proposed labeling changes based on four efficacy studies.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 14, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Jean Makie M.S., R.D., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Regulatory Project Management
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
11/28/03 09:50:56 AM
Chief, Project Management Staff



NDA 20-771
NDA 21-228

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

Dear Mr. Shawaryn:

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

NDA Number	Drug Name
20-771	Detrol™ (tolterodine tartrate) Tablets
21-228	Detrol LA™ (tolterodine extended release) Tablets

We have received your submission dated April 19, 2002, received April 22, 2002, relative to pediatric labeling for the various formulations of tolterodine.

We have completed the clinical review of this submission and have concluded that it is premature to discuss the pediatric labeling for the various formulations of tolterodine.

If you have any questions, call Jennifer Mercier, Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

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

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/s/

Daniel A. Shames
6/7/02 11:56:11 AM



NDA 21-228
Pharmacia & Upjohn Company
Attention: Gregory Shawaryn
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol LA (tolterodine tartrate extended release capsules)

We also refer to your May 31, 2001, containing a Type A meeting request and a meeting package to discuss the Pediatric Written Request (with regard to trials one through three) issued by the Office on January 23, 2001.

We have reviewed the referenced material and have the following comments and recommendations. Your questions are included for reference.

- 1. Upon receipt of the Pediatric Written Request, Pharmacia & Upjohn evaluated the synopses and generated draft protocols. Upon generation of these protocols, we consulted with several experts in the field of pediatric urology and received significant feedback. This feedback was incorporated into the enclosed protocols in order that they satisfy the outline described in the Written Request and also provide the most useful information to the practicing physician. Does the Division agree that these protocols satisfy the Written Request?*

It is not possible for the Division to agree that these protocols satisfy the Written Request (WR). A decision agreeing that a particular study satisfies the terms of a WR is made only by CDER's "Pediatric Exclusivity Board" after the study reports have been submitted for review.

After a Written Request has been sent to a sponsor, changes to the WR may be accomplished only through a formalized amendment process. This amendment process is laid out in the text of the original WR letter.

Alternatively, you may opt to pursue obtaining a Written Agreement (WA) with the FDA that sets forth a more detailed plan designed to address specific terms of the WR. The purpose of a WA is for clarification of the term(s) of the WR, such as those which may be subject to different interpretations or those which are confusing. You are advised that it is rare to obtain a WA from the FDA and it is a time-consuming endeavor. WA provide more detail and may make it harder for you to meet the term(s) of both the WR and the WA. You are referred to the issued WR for instructions regarding submitting a proposed WA. Please note that both WRs and WAs are issued only by the Office Director.

The protocols employ a dose escalation scheme that at the highest dose would provide tolterodine liquid 0.012 mg/kg/day in the 1 month-4 year and 5-10 year age groups. For the 11-15 year old group, the highest dosage is tolterodine extended release 6 mg once a day. Is this acceptable to the Division?

The drug products to be used in the protocols (including specific absolute doses) are clearly defined in the Written Request. Specifically, the Written Request Study #1 in patients aged one month to four years states: "The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.2-2 mg that will be administered orally in divided doses". The Written Request Study #2 in patients age five to ten years states "The patient's clinician will select the appropriate total daily dose for each patient within the range of 0.5-4 mg that will be administered orally in divided doses". The Written Request Study #3 in patients aged eleven to fifteen years states "The patient's clinician will select the appropriate total daily dose for each patient within the range of 2-4 mg." These absolute doses (i.e., in mg) will yield different weight-adjusted doses (i.e., in mg/kg) depending on the weights of the pediatric patients.

Please note that the Written Request clearly states that the "patient's clinician will select the appropriate total daily dose for each patient" within a pre-specified range of doses.

We remind you that if any item in the Written Request differs from the relevant study report submitted to CDER's "Pediatric Exclusivity Board", exclusivity may not be granted.

- 2. The treatment phase of these protocols is expected to be 3 months and enrollment is expected to be slow, especially in the very young patient group. Although we are planning to submit the required documentation by the specified date, we would like to discuss the possibility of an extension for 1 or more of the study reports. Under what conditions would it be possible to amend the Written Request to extend the due date for study reports to satisfy the Written Request?*

You are again referred to the issued WR for instructions regarding submitting proposed changes to the WR. Amendments to the WR, including timeframes for submitting the reports, will be considered however be aware that the formalized amendment process may be time-consuming and may not ultimately result in changes to the WR.

- 3. These studies employ cardiac monitoring and pharmacokinetic analysis which we believe will clearly define these parameters in the pediatric population. Would these data satisfy the Division's goals for the 4 trials in the Written Request?*

See Response to Question #1.

- 4. It is our understanding that submission of a completely developed liquid formulation is not required to satisfy the conditions of the Written Request. Is this correct?*

Again, the drug product to be used has been clearly delineated in the Written Request. Specifically, the Written Request for Study #1 states: "The drug product to be used in this study is tolterodine

syrup". The Written Request for Study #2 states: "The drug product to be used in this study is the following currently commercially not available formulation: tolterodine syrup".

Again, for purposes of obtaining additional exclusivity, if any item in the Written Request (including formulation) differs from the relevant study report submitted to CDER's "Pediatric Exclusivity Board", exclusivity may not be granted.

5. *Reference is made to the teleconference with the division held on May 15, 2000 and the meeting minutes issued by the Division on June 9, 2000. It is our understanding from these discussions that if the liquid formulation is shown to be bioequivalent to the immediate release tablets, a long term safety study is not required to register the liquid formulation under NDA 20-771. Does the Division agree with this understanding?*

For purposes of obtaining additional exclusivity, the required information has already been laid out in the WR.

If you are proposing a supplemental NDA to NDA 20-771 based on a potential formulation change to Detrol immediate release tablets, then a more detailed proposal for such a program should be submitted to NDA 20-771. Additional advice can be given after review of such a proposal.

6. *On May 14, 2001, Pharmacia and Upjohn responded to the Division's comments regarding protocols 583E-URO-0084-20 and 21. Are there any further outstanding issues relative to the combination of these protocols satisfying the Division's goal for trial 4 in the Pediatric Written Request?*

The requirements for Study #4 were delineated in the WR. The Division is unable to agree that the combination of protocols 583E-URO-0084-20 and 583E-URO-0084-21 "satisfy the Division's goal for Study #4". A decision agreeing that a particular study satisfies the terms of a WR is made only by CDER's "Pediatric Exclusivity Board" after the study reports have been submitted for review, and if any item in the Written Request differs from the relevant study report(s) submitted to CDER's Pediatric Exclusivity Board, exclusivity may not be granted.

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

Sincerely,

{See appended electronic signature page}

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Allen

7/27/01 04:01:28 PM



NDA 21-228

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

Dear Mr. Shawaryn:

We received your May 31, 2001 correspondence on June 01, 2001 requesting a Type A meeting to discuss protocols generated to satisfy the Pediatric Written Request issued by the Division on January 23, 2001.

We considered your request and have concluded that the requested meeting is not a Type A and is not necessary at this time. The Division will provide responses to your questions in writing as soon as possible. If you feel then that additional clarification is required, please submit a follow up meeting request with your specific questions.

If you disagree with our decision, you may discuss the matter with Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fn1.htm>.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
6/14/01 11:59:46 AM

**Division of Reproductive and Urologic Drug Products
Industry Teleconference Meeting Minutes**

Sponsor: Pfizer Incorporated
NDA: 21-228/S-006
Drug: Detrol[®] LA (tolterodine tartrate) 2 mg and 4 mg
Extended Release capsules
Date: 27 February 2004
Location: 6B-45 Conference Room
Time: 11:30 am – 11:45 am
Type: Information Request

FDA Attendees:

Stephan Ortiz, R.Ph., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer,
Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Jean Makie, R.D., MS, Senior Regulatory Project Manager, DRUDP (HFD-580)
Albert Perrine, RN, BSN, Regulatory Project Manager, DRUDP (HFD-580)

Pfizer Attendees:

Neil Mackillop, M.D., Clinical Development Director, Clinical Operations, Pfizer, Inc.
Bimal Malhotra, Ph.D., Associate Director, Clinical Sciences, Pfizer, Inc.
Amanda Dareker, Statistician, Clinical Operations, Pfizer, Inc.
Ulla Bengtsson, Statistician, Quintiles (contractor)
Ted Grasela, Statistician, Cognigen (contractor)
Paul Damiani, Global Regulatory Leader, Regulatory Affairs, Pfizer, Inc.
Helene Panzer, Ph.D., Team Leader, US Regulatory Affairs, Pfizer, Inc.
Tara Feehan, Manager, US Regulatory Affairs, Pfizer, Inc.

Background:

This teleconference was scheduled at the request of the Division to discuss submission of the complete data sets from the two population pharmacokinetic protocols used to generate the pooled data provided in supplement S-006 on October 10, 2003.

Discussion:

DRUDP requested that the sponsor submit the complete data sets for Protocol 53351 (studies 018 and 044) entitled "Pharmacokinetics of Oral Tolterodine in Children" and Protocol 53352 (studies 008 and 020) "Population Pharmacokinetic, Pharmacodynamic, and Safety Analyses of Tolterodine and its Metabolite DD 01."

Agreement:

Pfizer will electronically submit the complete data sets for the population pharmacokinetic studies during the week of March 1, 2004.

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/s/

Margaret Kober
3/5/04 03:42:59 PM

Status Meeting Minutes

NDA: 21-228/S 006

Drug: Detrol LA

Sponsor: Pfizer, Inc.

Date: February 9, 2004

Time: 2:30 – 3:30 PM

FDA/CDER/DRUDP Attendees:

Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)

George Benson, M.D., Urology Medical Team Leader, DRUDP

Lisa Soule, M.D., Medical Reviewer, DRUDP

Olivia Johnson, M.D., Medical Reviewer, DRUDP

Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, DRUDP

DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP

Stephan Ortiz, Ph.D., Clinical Pharmacology Reviewer, DRUDP

Jean Makie, M.S., R.D., Project Manager, DRUDP

Background: This was the four-month status meeting for NDA 21-228/ S 006 for Detrol LA (tolterodine tartrate extended release capsules).

- This submission, which was submitted on October 10, 2003 and received on October 14, 2003, contains pediatric efficacy studies, including PK and proposed labeling (for NDA 21-228 only; proposed labeling was not submitted to NDA 20-771), and also serves as the sponsor's submission of pediatric study reports and their request for determination of pediatric exclusivity.
- At the same time, the sponsor also submitted a general correspondence letter to NDA 20-771 to reference their NDA 21-228 submission of pediatric study results to satisfy the Written Request for Pediatric Studies issued by DRUDP jointly to both NDAs.
- The submission does not contain any new CMC or pharmacology/toxicology information.
- This is a priority review. The user fee goal date is April 14, 2004. The BPCA Clinical and Clinical Pharmacology Summary is due April 9, 2004.
- The Pediatric Exclusivity Board met on January 5, 2004, and granted an additional 6-month exclusivity for both NDA 21-228 and NDA 20-771.
- A final medical and clinical pharmacology summary from the Division must be completed for posting on the FDA's Pediatric web site by April 9, 2004 (day 175).

Issues Discussed: The following issues were discussed during this status meeting:

Clinical

The following are ongoing review issues:

- The review is on going.
- NDA 21-228 labeling regarding the lack of efficacy in children will be a review issue.
- The sponsor did not submit a revised label for NDA 20-771 (Detrol) as part of their submission of pediatric study reports and their request for determination of pediatric exclusivity. The need for revised labeling for Detrol will be a review issue.

Clinical Pharmacology and Biopharmaceutics

The following are ongoing review issues:

- The review is on going.

Pharmacology/Toxicology

- The submission does not contain any new pharmacology/toxicology information.
- The reviewer would like the sponsor to clarify the following:

“Submit the datasets associated with the 2 Population PK studies (as compared to the one pooled PK dataset that was submitted): 5.3.3.5.1 Studies 018 and 044 – “Pharmacokinetics of Oral Tolterodine in Children: Pooled Population Analyses of Data from Studies 018 and 044” and 5.3.3.5.2 Studies 008 and 020 – Population Pharmacokinetic, Pharmacodynamic, and Safety Analyses of Tolterodine and its Metabolite, DD 01, using data collected from pediatric patients enrolled in Protocols DETAPE-0581-008 and 583E-URO-0084- 020”.

Chemistry

- The submission does not contain any new CMC information.

Statistics

- The review is on going. No new issues have been identified at this time.
- The reviewer would like the sponsor to clarify the following:

“Do you have a flag for those individuals who are part of the Per Protocol Population (PP)? Somehow, in study 020, they could not be found for it and so far it is a laborious process to recode without the complete data definition.

Also, the initial review of the number of observation in effmcpp2.xpt doesn't match with the number in your result section with regards to the number of per protocol population size.”

Teleconference Minutes

Date: November 29, 2000 **Time:** 9:00-9:45 AM, EDT **Location:** Parklawn; 17B-43

NDA 21-228 **Drug:** tolterodine extended release **Indication:** overactive bladder

Sponsor: Pharmacia and Upjohn Company

Type of Meeting: Guidance

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

External Lead: Greg Shawaryn, Regulatory Manager, Pharmacia & Upjohn (P&U)

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

FDA Attendees:

Daniel Shames, M.D. - Deputy Director, DRUDP (HFD-580)

Mark Hirsch, M.D. - Medical Officer, DRUDP (HFD-580)

Brenda Gierhart, M.D. - Medical Officer, DRUDP (HFD-580)

George Benson, M.D. - Medical Officer, DRUDP (HFD-580)

Ashok Batra, M.D. - Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Biopharmaceutics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP

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

External Participants:

Gregory Shawaryn - Regulatory Manager, P&U

Mark Monnebach - Associate Director, Regulatory Affairs, P&U

Anneka Ohlsen - Director, Regulatory Affairs, P&U

Birgitta Ollsson - P&U

Ingrid Wallenbeck - P&U

H. De Koning Gans, M.D. - Vice President, Urology Research

Meeting Objective: To discuss Detrol's pediatric plan.

Background: P&U submitted a pediatric written request on June 28, 2000, as Supplement 005 to NDA 21-228. The agenda for this teleconference, which included three topics for discussion (Goessl's pediatric tolterodine article, NDA 21-228's Pediatric Rule and tolterodine draft Pediatric Written Request) was faxed to the sponsor prior to the teleconference for ease of discussion (see Appendix).

Discussion:

- DRUDP clarified requirements concerning the Pediatric Rule and the Written Request for Pediatric Exclusivity
 - the requirements to comply with the Pediatric Rule will be outlined in the action letter, and are not as detailed as those stated in the Written Request
 - the sponsor must comply with all the studies requirements stated in the Pediatric Written Request to obtain Pediatric Exclusivity
 - proposed Written Request will be submitted to the Pediatric Committee for recommendations, next week
 - the sponsor may initiate studies prior to receiving the Written Request from FDA at their own risk; to obtain Pediatric Exclusivity, the sponsor must comply exactly with the requirements stated in the Written Request
 - DRUDP will require the same studies from P&U to comply with the Pediatric Rule and the Written Request; the due dates will also be the same
- regarding the waiver for pediatric patients under five years of age requested by the sponsor, DRUDP stated the following:
 - the article by Goessl et al [Efficacy and Tolerability of Tolterodine in Children with Detrusor Hyperreflexia, Urology 55 (3), 2000], which is referenced in Drug Dex Drug Evaluations, contains pediatric dosing information and recommendations for children three months to 15 years of age
 - there is a concern that practitioners are obtaining information on pediatric dosing which is not included in the Detrol label, and may use Detrol in very young patients
 - a waiver for studies in pediatric subjects less than five years of age will not be given
 - a waiver for pediatric studies will be given for neonates (i.e., up to one month of age), and a deferment for other age groups
- regarding a pediatric formulation, DRUDP stated that a liquid formulation is recommended for the pediatric studies
 - P&U indicated that there is no currently available liquid formulation
 - P&U indicated their willingness to attempt to develop a syrup formulation to comply with the Pediatric Rule requirements
- the following clarifications and comments concerning study #1 in the draft Written Request were stated:
 - DRUDP recommends that sponsor conduct urodynamic testing in a subset of pediatric subjects with neurogenic detrusor hyperreflexia
 - pediatric patients aged 11 to 15 years should be included in the study to obtain information in this age group
 - PK sampling should be done in a few patients to show tolterodine's behavior in the 11 to 15 years age group; the analysis could be qualitative rather than quantitative
 - the sponsor may start Study #1 in the older age pediatric patients using the extended release formulation, while developing a syrup formulation to be used in the younger pediatric population
 - the Agency may split Study #1 into three studies
 - the extended release formulation was not included in this study because there is concern that patients with neurogenic bladder may chew the extended release tablet, and not be able to swallow it whole as intended; the sponsor clarified that the capsules could be opened and the pellets sprinkled on apple sauce; if pellets were used, the sponsor should provide data of food effect on pellets, and how the pellets compare to the intact capsule
 - the sponsor indicated that the PK/PD profile of tolterodine in pediatric subjects may be different from that in adults

- the following clarifications and comments concerning Study #2 in the draft Written Request were stated:
 - because the main concern with this study is the inability of the patients to swallow the capsule whole, the use of syrup is recommended
 - objective #2 will be changed to sparse PK sampling
 - the sponsor stated the following regarding Study #2: the study includes a 12-month safety extension; PK sampling will be descriptive only, and advanced population PK studies will not be performed; additional sampling will be conducted at the end of the 12-weeks period to better understand the drug's behavior in this age group; pediatric patients with overactive bladder due to non-neurogenic causes will be excluded; and that the sponsor is presently ready to start this study in Europe using the extended release capsule
 - the Agency clarified that only a 12-week Safety extension will be requested in Study #2

Decisions made:

- the draft Written Request will be presented to the Office Deputy Director, Dr. Victor Raczkowski, and to the Pediatric Committees for review and recommendations
- the sponsor agreed to attempt to develop a liquid formulation for tolterodine
- a Written Request will be sent to the sponsor outlining the studies necessary to obtain Pediatric Exclusivity
- in Study #2, the sponsor will consider the inclusion of pediatric patients who have swallowing difficulties, as well as providing additional instructions on how to help these patients swallow the capsule contents
- the requested waiver for studies in pediatric patients younger than 5-years of age for NDA 21-228 will not be granted
- a waiver for studies in neonates (i.e. birth to one month of age) will be granted
- a deferment for the studies in infants (one months to two years), children (2 years to 12 years) and adolescents (12 years to 15 years) will be given

Action Items:

- recommendations and comments from the Pediatric Committees (PDiT and Pediatric Pharmacokinetics) will be provided to the sponsor when available
- minutes of this teleconference will be faxed to sponsor within 30 days

Minutes Preparer

Concurrence, Chair

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

NDA 21-228

Teleconference Minutes November 29, 2000

Page 4

cc:

Original IND

HFD-580/DivFile

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

drafted: erf/ 12.13.00

concurrence: Shames 12.22.00/Hirsch/Gierhart 12.18.00/Benson 12.18.00/Batra/Parekh/Rumble 12.18.00

final: erf/12.22.00

MEETING MINUTES

Appendix

Topics for Discussion: Tolterodine Pediatric Studies

Teleconference with Pharmacia & Upjohn

November 29, 2000

- I. Pediatric Tolterodine Article by C. Goessl et al. Efficacy and Tolerability of Tolterodine in Children with Detrusor Hyperreflexia. *Urology* 55: 414-418, 2000.
- II. NDA 21-228 Pediatric Rule (tolterodine extended release capsules)
 - A. Requested waiver for pediatric patients under age 5
 - B. Waiver for newborn pediatric patients
 - C. Syrup formulation
 - D. Required studies and due dates
- III. DRAFT Tolterodine Pediatric Written Request

Study #1:

Type of study:

Pharmacokinetic (PK) and pharmacodynamic (PD [urodynamic]), effect, and safety study

Objectives:

1. To evaluate the pharmacokinetic profiles of Detrol® (tolterodine tartrate) syrup or tablets in pediatric patients with detrusor hyperreflexia due to neurogenic conditions on stable divided daily doses of tolterodine.
2. To evaluate tolterodine dose-effect (urodynamic) and concentration-effect (urodynamic) in order to establish one or more safe and effective tolterodine dosage regimens in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.
3. To evaluate the effect and safety of Detrol® (tolterodine tartrate) syrup or tablets in pediatric patients with detrusor hyperreflexia due to neurogenic conditions.

Indication:

Detrusor hyperreflexia due to neurogenic conditions

Study design:

Repeated dose, multiple-dose level, open label, minimum 2-week duration, PK and PD, effect and safety study.

For patients receiving tolterodine, the baseline urodynamic evaluation will be performed after a 3-7 days washout period off medication. Urodynamic evaluation will be repeated after a minimum of 2 weeks of treatment with tolterodine.

Age group in which study will be performed:

Ages one month to fifteen years divided into three subgroups: 1) ages one month to four years, 2) ages five to ten years, and 3) ages eleven to fifteen years.

Number of patients to be studied:

Enroll approximately 45 patients to have a minimum of eight patients in each of the three age subgroups for describing the PK/PD profile.

Study endpoints:

1. PK: appropriate stereospecific analysis of tolterodine and DD 01 metabolite plasma profiles; the sampling should be adequate to characterize the complete pK profile in this age group
2. Appropriate urodynamic evaluation: this may include maximal bladder capacity, intravesical pressure at maximal bladder capacity, and detection of uninhibited detrusor contractions.
3. Dose (in mg per kg)-effect (urodynamic) and concentration-effect (urodynamic)
4. Diary data to include number of micturitions per 24 hours and number of incontinence episodes per day
5. Safety: appropriate monitoring of adverse events, urodynamic, cardiovascular and laboratory parameters
6. Safety: Number of patients terminated prematurely

Drug information:

The drug product to be used in this study is the following commercially available formulation: Detrol® (tolterodine tartrate) Tablets, 1 or 2 mg OR a tolterodine syrup formulation. A total daily dose of 0.5–4 mg will be administered orally divided into two doses.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents.

Statistical information:

1. PK: Descriptive stereospecific analysis to include reporting of AUC, C_{max} , t_{max} , and $t_{1/2}$ for tolterodine and DD 01.

2. Urodynamic: Urodynamic measurements to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
3. Effect: Number of micturitions per 24 hours and number of incontinence episodes per day (diary data) to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
4. Safety: Safety measurements are to be tabulated. All participants who received at least one dose of study medication are to be included in the summaries and listing of safety data.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

Report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Study #2:

Type of study:

Clinical efficacy, PK, and safety study

Objectives:

1. To document the safety and tolerability of Detrol® (tolterodine tartrate) syrup or tablets in pediatric patients with overactive bladder.
2. To evaluate the PK of Detrol® (tolterodine tartrate) syrup or tablets in pediatric patients.
3. To evaluate dose-effect (diary data) and concentration-effect (diary data) in order to establish one or more safe and effective dosage regimens in pediatric patients with overactive bladder.

Indication:

Overactive bladder

Study design:

Minimum 12-week, double blind, two parallel group, two-to-one randomized, placebo controlled, clinical efficacy and safety study followed by a minimum 12-week, safety extension study.

Age group in which study will be performed:

Ages five to ten years

Number of patients to be studied:

Enroll approximately 300 patients, with approximately equal age distribution, to ensure a minimum of 100 patients completing 24 weeks of treatment with Detrol® (tolterodine tartrate) syrup or tablets.

Study endpoints:

1. *Primary endpoint:* change from baseline in number of incontinence episodes per week after 12 weeks treatment. *Other endpoints:* the change from baseline in mean number of micturitions per 24 hours after 12 weeks treatment, the change from baseline in mean urinary volume voided per micturition after 12 weeks treatment, and appropriate stereospecific analysis of tolterodine and DD 01 metabolite plasma.
2. Dose(in mg per kg)-effect (diary data) and concentration-effect (diary data)
3. Safety: incidence and severity of adverse events, postvoid residual urine, cardiovascular and laboratory abnormalities
4. Safety: Number of patients terminated prematurely from the trial

Drug information:

The drug products to be used in this study are the following formulations: Detrol® (tolterodine tartrate) syrup or tablets administered orally twice a day.

Drug specific safety concerns:

Monitoring of tolerability with special emphasis on the gastrointestinal tract and expected side effects of anticholinergic agents (e.g. constipation, dry mouth).

Statistical information:

1. All statistical tests will be two-sided and the level of significance will be 0.05.
2. PK: Appropriate descriptive stereospecific analysis for drug and metabolite.
3. Micturition Diary Data: Diary data are to be tabulated as a function of dose (mg/kg). Baseline measurements will be contrasted with on treatment measurements.
4. Safety: Safety measurements are to be tabulated by treatment group, body system and preferred term for both 12 week efficacy and 12 week safety extension trials. All participants who received at least one dose of study medication are to be

included in the summaries and listing of safety data. Patients with abnormal postvoid residual urine findings or Serious Adverse Events will be reported on a case-by-case basis.

Labeling that may result from the study:

Appropriate changes to the label to incorporate the study results will be made.

Format of reports to be submitted:

A final study report will be submitted. We recommend that you follow the July 1996 ICH (E3) guideline for structure and content of clinical study report. The final study report will address the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the study:

Report of the above study must be submitted to the Agency on or before December 15, 2002. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Critical Analyses:

1. Provide a critical analysis of urodynamic data in adults with detrusor hyperreflexia treated with tolterodine. This will be submitted with the final study reports. The analysis will review clinical trial data and the published literature and will describe the dose-effect (urodynamic) of tolterodine.
2. Provide a critical analysis of tolterodine safety in pediatric patients. This will be submitted with the final study reports.

/s/

Evelyn Farinas
12/22/00 11:25:07 AM
CSO

detrol la tcon 11/29

Daniel A. Shames
12/22/00 02:31:18 PM
MEDICAL OFFICER

Teleconference Minutes

Date: May 15, 1999 **Time:** 11:30-1:00 PM EST **Location:** PKLN; 17B43

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

Sponsor: Pharmacia & Upjohn

Type of Meeting: Guidance

Meeting Chair: Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

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

FDA Attendees:

Victor Raczkowski, M.D. – Deputy Director, Office of Drug Evaluation III (HFD- 103)

Bronwyn Collier, B.S.N. – Associate Director for Regulatory Affairs, Office of Drug Evaluation III (HFD-103)

Marianne Mann, M.D. – Deputy Director, DRUDP (HFD-580)

Daniel Shames, M.D. – Medical Team Leader, DRUDP (HFD-580)

Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
@ DRUDP (HFD-580)

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

Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Lead: Gregory G. Shawaryn, Regulatory Manager, Global Regulatory Affairs

External Participants:

Hendrik De Koning Gans – Vice President, Product Development, Urology

Annika Ohlsson – Director, Global Regulatory Affairs

Gregory G. Shawaryn - Regulatory Manager, Global Regulatory Affairs

Birgitta Olsson – Clinical Pharmacology

Ingrid Wallenbeck – Clinical Program Leader, Urology

Meeting Objective: To discuss specific questions submitted by sponsor regarding pediatric exclusivity.

Background: At the August 12, 1999 teleconference, the sponsor requested guidance on the use of Detrol in patients 18 years of age and younger, inclusion of prescribing information for pediatric patients in the labeling, adequacy of data to support pediatric exclusivity and pediatric studies submission. At that time, the Division recommended that the sponsor not initiate pediatric studies nor make suggestion in the labeling of pediatric use until the potential QT prolongation association with the use of Detrol was resolved. The Division also provided general comments regarding dosing, age group selection, formulation and number of patients of future pediatric studies. In December 1999, the sponsor was notified that plans for pediatric studies could start. The sponsor is now requesting a Type A meeting with the Division, to discuss their

proposal for the Division's request for a pediatric study. This submission (dated April 12, 2000) includes study summaries for two proposed protocols [583URO0084-018 (pediatric PK study in subjects aged 11-17 years) and 98-OATA-061 (pediatric efficacy study in subjects aged 6-10 years)], the full study report of protocol 97-OATA-044 (pediatric PK study in subjects aged 5-10 years) and specific questions for the Division's comments. An additional question for consideration at the teleconference of May 15, 2000 was submitted on April 24, 2000.

Discussion:

Division's general comments:

- intent of teleconference is to provide comments and clarify plans regarding pediatric exclusivity issues
- the Division would like clarification from sponsor regarding:
 - type of formulations proposed for use in pediatric patients (i.e., immediate release, controlled release and oral liquid)
 - dose proposed for pediatric patients
 - age groups for each study
 - indication statement

Sponsor's responses:

- the proposal to obtain Pharmacokinetic data in neurogenic bladder patients resulted from a previous suggestion made to the sponsor by the Division
- the selection of a 5-10 years old group for Protocol 97-OATA-044 was based on the potentially greater exposure to tolterodine in this group than in older pediatric patients
- it is expected that all dosage forms will be interchangeable in terms of safety and efficacy
 - liquid formulation is being considered for ease of swallowing in younger aged pediatric subjects and in the elderly population
- it is the sponsor's intent to conduct pediatric studies with one formulation, and also obtain information applicable to all, so that pediatric statements would be included in the label for all formulations
 - the sponsor will consider the Division's suggestion to provide information broken down by formulation, indication, dose, and to justify each dose and formulation
 - the sponsor may decide at a later time to pursue only one formulation
- the proposed indication is that of urge incontinence, based on either detrusor instability or neurogenic disease; sponsor plans to focus on overactive bladder with incontinence as the endpoint; indication statement in pediatric subjects will be the same as that for adult subjects

Additional discussion:

- age groups:
 - the Division recommends that the age group for 583URO0084-018 include patients 11 to 15 years old, inclusive
 - the Division may want to see information in pediatric subjects under 5 years of age for Pediatric Exclusivity, depending on desired indication
 - Pediatric Rule requires that the sponsor conduct studies in all four pediatric age groups or request waiver and provide justification for exclusion of certain age groups; the pediatric age groups for the purpose of Pediatric Rule studies are defined as neonate (birth to 1 month), infant (1 month to 2 years), child (2 to 12 years), and adolescents (12 years to <16 years)
 - the sponsor asked if it would be sufficient to conduct studies on a limited number of younger pediatric subjects to confirm that no further dose adjustment is needed
 - the sponsor may provide the background and research regarding the population of younger pediatric subjects treated for GU reflux, high pressure voiding, and send a rationale for pediatric studies; alternatively, the sponsor could also request a waiver to exclude certain age groups and provide the rationale for this request

- Study with pediatric subjects under 5 years of age:
 - the sponsor will consider the feasibility of PK studies for this age group, in particular those with GU reflux
- Pediatric Exclusivity and Pediatric Rule:
 - under the Pediatric Exclusivity, after receiving a Written Request for pediatric studies, the sponsor should submit studies that are necessary to round out the existing gaps in the label; this submission is voluntary and is made in response to a written request issued by FDA; if granted, exclusivity applies to drug products containing the active moiety (i.e., tolterodine)
 - under the Pediatric Rule, pediatric studies may be required; this submission is mandatory but applies only to the application or supplement under consideration for adults
 - waivers, partial waivers and deferrals, apply to Pediatric Rule, not to Pediatric Exclusivity
 - sponsor indicated that the purpose of the teleconference was to discuss Pediatric Exclusivity for Detrol

General Pediatric Program Questions:

Question #1: The sponsor would like to confirm the request from the Agency for long-term data as briefly discussed at the teleconference dated August 12, 1999. At this time the Agency requested that at least 100 children (aged 5-10) should be treated for 3 months with 3 additional months follow-up data. Would 100 children treated for 6 months be sufficient?

- yes, the Division agrees with the proposed trial design, with the following additional comments:
 - additional clarification is needed to determine what age groups and from which protocols the pediatric subjects would be included in the open-label extension study
 - Proposed Protocol 98-OATA-061 is in pediatric subjects aged 6-10 years; the Agency requested at least 100 children aged 5-10 years; the Sponsor should consider changing ages of 98-OATA-061 to pediatric subjects aged 5-10 years

Question #2: Would this program be sufficient to qualify for pediatric exclusivity?

- the Division cannot answer this question until a Proposed Pediatric Study Request (PPSR) is submitted and reviewed, and a Written Request is issued by FDA
- further discussion may be necessary
- it appears that the sponsor is heading in the correct direction

Question #3: Would this program also satisfactorily fulfill the requirement for pediatric studies/program described in the acknowledgement letter for NDA 21-228 issued by the Division on March 1, 2000?

- further discussion is necessary
- the sponsor may want to add a study in younger aged pediatric subjects with GU reflux
- regarding Pediatric Rule, sponsor needs to study all four pediatric age groups or request waivers (or partial waivers) and provide justification for exclusion of certain age groups

Proposed 583URO0084-018 (pediatric PK study in subjects aged 11-17 years) Questions:

Question #1: For ethical reasons, we have not included a placebo treatment in this study. We will, however, keep the study blinded with regard to which tolterodine dosage is given (2 or 4 mg). Is this acceptable?

- yes, it is acceptable not to include a placebo treatment in this study
- if sponsor plans to request neurogenic bladder indication, a placebo controlled efficacy study would be necessary

Question #2: Also for ethical reasons we do not plan to measure trough levels (Cmin) on the days proceeding Day 7. We know from a study with the PR capsule in adults (98-TOCR-006-included in NDA 21-228) that steady state is reached after 4 days. The study in children aged 5-10 years (98-OATA-044) showed that $t_{1/2}$ is the same in children and adults. This supports that steady-state will be reached at the same time in children. Does the Division agree that trough levels would not need to be measured until Day 7?

- the Division has safety concerns with administration of the 4 mg dose
- the Division recommends that sponsor conduct a two-step approach, which includes an evaluation of lower doses before proceeding to the 4 mg dose
- if there are no safety problems with doses up to 4 mg dose, then it is acceptable not to measure trough levels over 7 days
- sponsor should provide their justification for believing that the PK is similar in children and adults
- sponsor agrees with the two-step approach

Question #3: The study in children 5-10 years old showed the same pattern for the metabolites that we see in adults. We will therefore not measure other serum metabolites other than DD 01 in this study. Is this acceptable?

- yes, it is acceptable to measure only the DD01 metabolite in Protocol 583URO0084-018

Question #4: There will be an open-label extension study with the objective to study long-term safety. Each patient will be offered to continue on the highest dose that he/she has tolerated. Is this acceptable?

- yes, it is acceptable
- sponsor clarified that the original intent was for the Protocol 583URO0084-018 patients who tolerated the drug to enter the open-label extension study, at the highest tolerated dose; this may be revised

Question #5: We are aware that this patient group has a tendency for increased residual volume. In this protocol we suggest a residual volume below 25 ml for inclusion. An alternative strategy would be a fixed residual fraction (residual a per cent of functional capacity). Does the Division believe a fixed volume or a relative volume would be the more appropriate entry criteria?

- this issue needs further discussion and clarification
- the Division has the following additional comments:
 - a justification and references are needed for fixed versus relative volumes, for justification and reference for formula to calculate bladder capacity, and for justification for using fixed volume in this protocol and relative volume in the 98-OATA-061 protocol
- relative volume may be more appropriate for Protocol 583URO0084-018 in the smaller stature neurogenic bladder pediatric subjects, particularly those with spina bifida

Question #6: The Agency suggested evaluation of efficacy in both neurogenic and unstable bladder patients. Is it acceptable to uniquely evaluate the efficacy in neurogenic patients with urodynamic parameters in this study?

- it is acceptable from a Pharmacokinetic standpoint
- the results from the study will not be sufficient for a neurogenic bladder indication
- sponsor asked to provide details regarding urodynamic testing, i.e. if sponsor plans limited ultrasound urodynamic testing or urodynamics testing involving catheterization

Additional 583URO0084-018 discussion and comments:

- the Division has safety concerns with the administration of the 4 mg extended release dose; the concern is that a 4 mg dose in this age group could be the same as a 2-4 fold increase over adult exposure
- the Division recommends further safety evaluation before titrating to a 4 mg dose; of particular concern is the potential high exposure in poor metabolizers and the relatively small size of pediatric patients with neurogenic bladder or spina bifida
- the sponsor indicated that exposure in this age group from the 4 mg dose is expected to be only 2-fold that of the adult exposure
- the sponsor will consider a two-step approach, involving the administration of a 2 mg dose to this group, and evaluating for safety before proceeding with the 4 mg administration
- sponsor to consider eliminating pediatric subjects ages 16 and 17 years from proposed trial
- the Division recommends adding as an inclusion, urodynamically proven hyperreflexic bladder; "neurogenic lesions" are not defined; urinary frequency/urgency are not inclusions, subjects with hypotonic bladders should not be in trial and should be eliminated with residual urine exclusion
- the Division recommends adding as an inclusion criteria that patients have no evidence of clinically significant urinary tract infection at entry to trial
- schedule of events lists "urine sampling"; the Division recommends urinalysis and urine culture be performed at Pretrial visit and urinalysis at Period 1 Day 7 and Period 2 Day 7 visits; the Division recommends performing urine culture before any urodynamic testing involving catheterization; sponsor asked to clarify if prophylactic antibiotics be given after any catheterization

Proposed 98-OATA-061 (efficacy study in subjects aged 6-10) Questions:

Question #1: For the Phase III pediatric study, ECGs are planned only at baseline to exclude major cardiac abnormalities and arrhythmias. No follow-up ECGs during tolterodine treatment are planned unless specifically indicated. Is this acceptable?

- no, it is not acceptable
- the Division recommends that follow-up ECGs be conducted in all pediatric subjects at steady state; subjects should be at steady state at Visit 3

Question #2: For ethical reasons, laboratory tests are planned only at entry of the Phase III pediatric study to confirm normal hepatic and renal function. Is this acceptable?

- no, this is not acceptable
- the Division recommends urine culture, urinalysis, CBC, chemistry panel at Visit 1 and at Visit 4 or an Early Discontinuation

Additional Protocol 98-OATA-061 discussion and comments:

- the Division finds the overall study design acceptable
- the dose selection of 2 mg extended release is reasonable; sponsor to consider dosing on a mg/Kg basis
- the Division believes that the study should yield adequate safety information if modified as described below
- the Division recommends that sponsor conduct sparse sampling to obtain additional Pharmacokinetic information in this population
- the sponsor will consider adding sparse PK sampling during the 12-week study period
- the Division recommends that ECGs be conducted in all pediatric patients at Visit #3 (i.e., at steady state), to establish a link with poor metabolizing status
- the sponsor indicated that because studies are international it may be difficult to standardize ECG procedures
- the sponsor will consider developing a plan that will include ECGs at baseline and a follow-up ECG at a later time in certain study sites, and provide a balance between poor metabolizers and normal metabolizers
- the Division recommends that CBC and Chemistry panel be done at Visit 1, and Visit 4 or at Early Discontinuation
- the Division recommends adding physical examination
- the Division recommends extending age eligibility to include age 5 years
- the Division recommends adding exclusion for ectopic ureteral insertion, continuous dribbling
- sponsor to consider adding inclusion for frequency and/or urgency to match adult indication
- sponsor asked to justify their exclusion of females post menarche
- sponsor asked to clarify if "damp clothing" incontinence will be recorded separately from incontinence requiring subject to change clothes; concern relates to differentiating incontinence from perspiration, especially in summer months

April 24 submission:

Would a bioequivalence study comparing the liquid formulation to the immediate release tablet be sufficient to clear this product for the market, or would an additional safety study be required?

- if the two formulations are not bioequivalent, additional safety and efficacy data will be needed
- the sponsor should provide information for each formulation, indication and age group
- the Division is concerned that the liquid formulation may demonstrate higher C_{max} and lower C_{min} than the immediate release tablet or the modified release
- sponsor to consider study in the pediatric age groups where liquid formulation is intended for use, i.e. under age 5 years

Additional question (May 15): Sponsor seeks guidance on how to fulfill the Pediatric Rule requirements for NDA 21-228, keeping within the time frame of 120 days as stated in the March 1, 2000 letter?

- the sponsor should submit the pediatric plan including the pediatric formulation and all age groups
- the sponsor may ask for a deferral, a waiver or a partial waiver if there is an age group that will not be relevant

Decisions made:

- further discussions are needed between the Division and the sponsor to move forward with Pediatric Exclusivity for tolterodine
- indication statement in pediatric subjects is anticipated to be the same as that for adult subjects
- treating 100 pediatric subjects for 6 months is acceptable (refer to question #1)
- it is acceptable to not include a placebo arm in Protocol 583URO0084-018 (refer to question #1 under Protocol 583URO0084-018)
- sponsor agrees with the two-step approach proposed by the Division regarding evaluation of safety after a 2 mg dose, before titrating to a 4 mg dose in the 11-17 years old group (refer to question #2 under Protocol 583URO0084-018)
- if there are no problems with the 2 mg dose, then it is acceptable to not measure trough levels during Day 7 (refer to question # 2 under 583URO0084-018)
- it is acceptable to measure only the DD01 metabolite in Protocol 583URO0084-018 (refer to question # 3 under Protocol 583URO0084-018), in addition to parent drug
- it is acceptable to offer patients to continue in an open-label extension study on the highest tolerated dose (refer to question # 4 under Protocol 583URO0084-018)
- it is acceptable from a Pharmacokinetic standpoint to uniquely evaluate the efficacy in neurogenic patients with urodynamic parameters; the results from the study will not be sufficient to support a neurogenic bladder indication (refer to question # 6 under Protocol 583URO0084-018)
- it is not acceptable to conduct ECGs only at baseline (refer to question #1 under Protocol 98-OATA-061)
- it is not acceptable to conduct laboratory test to confirm normal hepatic and renal function only at entry of the Phase 3 pediatric study (refers to question #2 under Protocol 98-OATA-061)
- if the liquid formulation is bioequivalent to the immediate release tablet, additional safety and efficacy data will be needed (refer to April 24 submission section)
- the sponsor will submit a pediatric plan to satisfy the Pediatric Rule requirements for NDA 21-228 (refer to additional question (May 15))

Action Items:

- Minutes will be provided to the sponsor within 30 days

Minutes Preparer

Chair

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

NDA 20-771
Teleconference Minutes May 15, 2000
Page 8
cc:
NDA Arch:
HFD-580/DivFile

HFD-580/Raczkowski/Allen/Mann/Shames/Gierhart/Huang/Parekh/Chatterjee/Rumble/Farinas

drafted: Farinas, 5.16.00

concurrence: Mann 5.24.00/Shames 6.08.00/Gierhart 5.26.00/Parekh 6.9.00/Rumble 5.19.00
/Raczkowski 5.29.00/Collier 5.24.00

final: Farinas, 6.9.00

Teleconference MEETING MINUTES

Teleconference Minutes

Date: August 12, 1999 **Time:** 9:00 AM **Location:** Parklawn 17B-43
NDA 20-771 **Drug:** Detrol (tolterodine) **Indication:** Bladder instability

Sponsor: Pharmacia & Upjohn

Type of Meeting: Guidance

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

External Lead: Gregory Shawaryn – Regulatory Manager, Regulatory Affairs

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

FDA Attendees:

Marianne Mann, MD – Deputy Director, DRUDP (HFD-580)
Daniel Shames, MD - Urologist, Team Leader, DRUDP (HFD-580)
Norman Marks, MD – Medical Officer, DRUDP (HFD-580)
Dena Hixon, MD – Medical Officer, DRUDP (HFD-580)
Terri Rumble, BSN – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)
Jeanine Best, MSN, RN - Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Soraya Madani – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

External Lead: Gregory Shawaryn, Regulatory Manager

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

External Attendees:

Hendrick De Koning Gans, MD – Vice President, Product Development, Urology
Susan Mondabaugh, Ph.D. – Director, Global Regulatory Affairs
Mark Mannebach, Ph.D. – Associate Director, Global Regulatory Affairs
Karin Brisman – Regulatory Manager, Global Regulatory Affairs, Sweden
Gregory Shawaryn – Regulatory Manager, Global Regulatory Affairs, US
Bengt Hallen, Ph.D. – Director, Clinical Pharmacology
Ingrid Wallenbeck, MD – Clinical Program Leader, Urology

Meeting Objective: To provide guidance on studies required for pediatric exclusivity

Background: The sponsor requested a meeting in a letter dated June 7, 1999, to discuss the following: a) use of Detrol (tolterodine) in patients 18 years of age and younger, b) inclusion of prescribing information for children in the labeling, c) literature citations concerning diurnal enuresis in children, d) adequacy of data to support extension of exclusivity per FDAMA, and

e) guidance on pediatric studies submission.

Discussion:

- sponsor provided an overview of results of study 97-OATA-044 in children; Division could not comment because the additional information on study 97-OATA-044 was not received with sufficient time prior to the teleconference to allow for its review
- Division clarified that pediatric studies could not proceed until the QT prolongation potential of Detrol was elucidated; sponsor noted that it would comply with Division's request although it is sponsor's belief that the QT prolongation does not occur with Detrol
- dosing, age group selection, formulation and assay validation of future pediatric studies were discussed; proposed dose is 1 mg twice a day; inclusion of older group of children, 11 to 17 years of age is planned for the future; pregnancy was mentioned as a potential concern in this older age group
- a liquid formulation is being developed, which would require bioequivalence studies; the analytical assay used will be the same as that used in adult studies
- an outline of the contents for a proposed pediatric study was addressed; Division indicated that at least 1 significant study was needed to show safety and efficacy in children; the sponsor should consider a study of 6 months duration, to include 100 or more children, with an age range from 5 to 16 years, and include a diverse population, stratified for disease, which may include poor metabolizers; study should be a 3-month placebo-controlled trial with 6-month follow up safety data; sparse plasma samples should be collected from subset population and sponsor should consider submitting information on total and unbound plasma concentration for both tolterodine (parent drug) and active metabolite, as well as performing population pharmacokinetic studies
- the regulations state that if the indication is the same as for adults, pharmacokinetic data alone is sufficient; however the Division would like to see at least an additional study as previously outlined due to concerns over long-term safety and the fact that children have a different disease process
- sponsor proposed a labeling update to include dosing information for children; rationale for this change is based on IMS data which indicates that off label use in children is common, existing pharmacokinetic differences between children and adults, and sponsor's concern that practitioners may administer an unsafe dose to children; Division agreed that labeling could include a statement indicating that children should not receive more than 1 mg twice a day, but indicated that the QT interval prolongation issue needs to be resolved prior to any suggestion of pediatric use in children
- sponsor requested clarification regarding any potential negative impact on pediatric exclusivity caused by early submission of the pharmacokinetic data on children from study 97-OATA-044; Division understands that updating the labeling as proposed would not result in penalties regarding pediatric exclusivity, but will check on this
- sponsor requested clarification on procedure for submission of pediatric exclusivity studies; Division provided broad guidelines, i.e., sponsor sends proposal of pediatric protocol to the Division, informal dialogue between sponsor and Division ensues to hone study details, Division sends written request to sponsor for a trial based on previous discussions

Decisions made:

- consideration will be given to updating the label to reflect safety dosage in children
- submission of early pharmacokinetic data to support a labeling update and its effects on pediatric exclusivity will be explored

- sponsor will not initiate pediatric studies nor make any suggestions in the labeling of pediatric use until the QT prolongation issue is resolved

Unresolved decisions: none

Action Items:

- minutes to be sent to sponsor within 30 days
- sponsor will submit a proposed pediatric study according to the general guidelines outlined by the Division; this will be submitted informally
- Division will clarify the requirements for pediatric exclusivity and address whether labeling changes based on PK data would affect claims for exclusivity

Minutes Preparer

Concurrence, Chair

cc:

Original IND HFD-580/DivFile

HFD-580/Rarick/Mann/Shames/Hirsch/Marks/Hixon/Parekh/Madani/Colangelo/Farinas/Rumble

drafted: erf/08.13.99

concurrence: MMann 08.19.99/DShames,Marks,Hixon 08.20.99/Parekh 08.25.99/Madani/LPauls for TRumble 08.18.99/Best 08.20.99

final: Farinas/08.31.99

MEETING MINUTES

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Advisory Committee Meeting

Not applicable for this application.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-228

DRAFT

Supplement Type (e.g. SE5): SE8

Supplement Number: 006

Stamp Date: October 14, 2003

Action Date: April 14, 2004

HFD 580

Trade and generic names/dosage form:

Tradename – Detrol LA

Generic: tolterodine tartrate

dosage form: 2 and 4 mg extended release tablets

Applicant: Pfizer Pharmaceuticals

Therapeutic Class: 1S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): _____

While the Sponsor does not submit labeling language specific to the pediatric population in the "Indications and Usage" section nor under the "Dosage and Administration" section of the labeling, as described in 21 CFR 201.57(f)(9), it appears to the review team that there is an implied pediatric indication sought, as evidenced by submission of pediatric PK data and language in the "Pediatric Use" section of the labeling. This will be a review issue.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: not applicable

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min X kg _____ mo. _____ yr. birth Tanner Stage _____
Max X kg _____ mo. 1 yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- X Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: Not Applicable

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other:

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min X kg _____ mo. 4 yr. _____ Tanner Stage _____
Max X kg _____ mo. _____ yr. 15 Tanner Stage _____

Comments: A Written Request (WR) letter dated January 23, 2001, asked Pfizer Inc. to perform four pediatric studies with tolterodine tartrate and to prepare two critical analyses. In the current electronic submission SE8-006, the sponsor has responded to the WR by submitting:

- a final study report, 583E-URO-0581-001 (Study #1 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in 8 patients ages one month to 4 years, with detrusor hyperreflexia due to neurogenic conditions),
- a final study report, 583E-URO-0581-002 (Study #2 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in approximately 15 patients ages five to ten years, with detrusor hyperreflexia due to neurogenic conditions),
- a final study report, 583E-URO-0581-003 (Study #3 in the Written Request, a pharmacokinetic, pharmacodynamic and safety study in approximately 15 patients ages eleven to fifteen years, with detrusor hyperreflexia due to neurogenic conditions),
- three final study reports, 583E-URO-0084-020, DETAPE-0581-008 and 583E-URO-0084-021 [Study #4 in the Written Request, a 12-week double-blind, two parallel group, placebo-controlled randomized clinical efficacy, pharmacokinetic and safety study with a minimum 12-week safety extension study in approximately 300 patients (to ensure a minimum of 100 patients completing 24 weeks of treatment) ages five to ten years, with overactive bladder], and
- two critical analyses.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/ Grace Carmouze

(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

110A 21-228

20-771

PELLS EXCLUSIVELY CHECKED

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 01/23/01 Application Written Request was made to: NDA#20-771 and 21-228
 Timeframe Noted in Written Request for Submission of Studies 10 / 15 / 03 (per March 3, 2003 Amended WR)
 NDA# 21-228 Supplement # 006 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
 Sponsor Pfizer (originally Pharmacia Upjohn)
 Generic Name tolderodine Trade Name Detrol LA
 Strength 2 and 4 mg Dosage Form/Route extended release tablets (oral)
 Date of Submission of Reports of Studies 10 /10 /03 (received 10/14/03)
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 1/12/04.

Was a formal Written Request made for the pediatric studies submitted?	Y <u>X</u>	N <u> </u>
Were the studies submitted after the Written Request?	Y <u>X</u>	N <u> </u>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y <u>X</u>	N <u> </u>
Was the timeframe noted in the Written Request for submission of studies met?	Y <u>X</u>	N <u> </u>
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y <u>X</u>	N <u> </u>
Did the studies fairly respond to the Written Request?	Y <u>X</u>	N <u> </u>

SIGNED *7152 M. Simola* DATE 12/12/03
 (Reviewing Medical Officer)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted** **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
<u>20-771/21-228</u>	<u>5382600</u>	<u>3/25/12</u>
<u>" "</u>	<u>5559269</u>	<u>11/5/13</u>
<u>21-228</u>	<u>NDF</u>	<u>12/22/03</u>

SIGNED *[Signature]* DATE 1/5/04

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Grace Carmouze
1/6/04 10:31:58 AM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: NDA 21-228 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Date of Application: October 10, 2003
Date of Receipt: October 14, 2003
PDUFA Date: April 14, 2004

Indication(s) requested: for the relief of symptoms of urinary frequency, urinary incontinence or urgency associated with overactive bladder

Type of Application: Full NDA _____ Supplement X
(b)(1) X (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S _____ P X
Resubmission after a withdrawal or refuse to file N/A
Chemical Classification: (1,2,3 etc.) 1S
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid X Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES X NO _____
User Fee ID# 4603
Clinical data? YES X NO _____ Referenced to NDA# 20-771

Date clock started after UN N/A

User Fee Goal date: April 14, 2004

Action Goal Date (optional) April 14, 2004

• Does the submission contain an accurate comprehensive index? YES NO

- Form 356h included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:
- If electronic NDA, does it follow the Guidance? YES NO
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? N/A YES NO
- Patent information included with authorized signature? YES NO
- Exclusivity requested? YES: If yes, 6 months (pediatric exclusivity) NO
 Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.
 Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix _____." Applicant may not use wording such as, "To the best of my knowledge,"
- Financial Disclosure included with authorized signature? YES NO
 (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
- If no, for what ages and/or indications was a waiver and/or deferral requested:
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A * YES NO

(*Drug Substance and Drug Product sections (with the exception of 3.2.P.2 Pharmaceutical Development) are cross-referenced to NDA 21-228 in the original submission dated February 25, 2000)

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date NO
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date NO
 If yes, distribute minutes before filing meeting.

NOTE: A Type C guidance teleconference was held on 11/29/00 to discuss the proposed pediatric written request submitted on 6/28/00

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?

*Tradename review not applicable with SE8; no new trade name requested. YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?

* This submission did not contain PPI or MedGuide YES NO

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO N/A

*This is not an application for an OTC product.

Advisory Committee Meeting needed? YES, date if known NO

Clinical

• If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO N/A

Chemistry

• Did sponsor request categorical exclusion for environmental assessment? YES NO

• If no, did sponsor submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) package submitted? YES NO*

• Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

CMC Summary Comments (taken from 12/1/03 CMC filing review): Even though there is a lack of chemistry information, this is a response to the Written Request for Pediatric Studies issued by DRUDP on 23-JAN-2001 and is fileable. It contains data from 10 clinical studies in order to obtain the pediatric exclusivity described in the Written Request. The CMC section of the supplement consists of only composition information on the clinical batches used in the pediatric studies. These batches include the currently approved extended release capsules and the immediate release tablets, as well as an investigational oral solution. The applicant references the currently approved NDAs 21-228 and 20-771 for all chemistry information on the extended release capsules and the immediate release tablets. The applicant does not intend to market the oral solution that was used in 3 of the 10 clinical studies. There is no change to the Description, Dosage, and How Supplied sections of the currently approved physician insert. Because there is no new formulation proposed for commercial distribution, the reference to chemistry information on the currently approved products of NDAs 21-228 and 20-771 is adequate, and the composition information on the investigational oral solution is adequate for the purpose of the investigation studies.

If 505(b)(2), complete the following: Not applicable

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
(Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?

If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

___ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

Filing Meeting Minutes

NDA: 21-228/S 006

Drug: Detrol LA

Sponsor: Pfizer, Inc.

Date: November 25, 2003

Time: 10:30 AM – 11:30 AM

FDA/CDER/DRUDP Attendees:

Donna Griebel, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP)

George Benson, M.D., Urology Medical Team Leader, DRUDP

Lisa Soule, M.D., Medical Reviewer, DRUDP

Brenda Gierhart, M.D., Medical Reviewer, DRUDP

DJ Chatterjee, Ph.D., Clinical Pharmacology Reviewer, DRUDP

Su Tran, Ph.D., CMC Reviewer, DRUDP

Jean Makie, Project Manager, DRUDP

Issues Discussed: On October 10, 2003, a supplemental (S 006) new drug application (NDA) was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol LA (tolterodine tartrate extended release capsules). At the same time, the sponsor also filed a general correspondence letter to NDA 20-771 to reference their NDA 21-228 submission of pediatric study results to satisfy the Written Request for Pediatric Studies issued by DRUDP jointly to both NDAs.

This submission, which was received on October 14, 2003, contains pediatric efficacy studies, including PK and proposed labeling (for NDA 21-228 only; proposed labeling was not submitted to NDA 20-771), and also serves as the sponsor's submission of pediatric study reports and their request for determination of pediatric exclusivity. The submission does not contain any new CMC or pharmacology/toxicology information.

This efficacy supplement is a priority review. The 60-day filing date is December 12, 2003, in accordance with 21 CFR 314.101(a). A 74-day filing letter is not required. If the application is filed, the user fee goal date will be April 14, 2004. The Pediatric Exclusivity Board will meet on January 5, 2004, to determine if the sponsor should be granted an additional 6-month exclusivity for both NDA 21-228 and NDA 20-771.

During this filing review meeting, the following issues were identified:

Clinical

The following are areas of concern and ongoing review issues:

- NDA 21-228 labeling regarding the lack of efficacy in children will be a review issue.

- The sponsor did not submit a revised label for NDA 20-771 (Detrol) as part of their submission of pediatric study reports and their request for determination of pediatric exclusivity. The need for revised labeling for Detrol will be a review issue.
- The application is filable.

Clinical Pharmacology and Biopharmaceutics

The following are areas of concern and ongoing review issues:

- The appropriateness of the sponsor's proposed labeling of the pediatric PK information for both Detrol LA and an experimental oral solution will be a review issue.
- The application is filable.

Pharmacology/Toxicology

- The submission does not contain any new pharmacology/toxicology information. No review issues noted at time of filing.

Chemistry

- The submission does not contain any new CMC information. No review issues noted at time of filing.
- The application is filable.

Statistics

- No review issues noted at time of filing. The application is filable.

Summary:

The Division finds this application filable. The user fee goal date will be April 14, 2004.

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Jean Makie
2/4/04 05:34:00 PM
CSO

Jean Makie
2/4/04 05:35:30 PM
CSO

**Screening of New NDA for Statistical Filing
Division of Biometrics II**

NDA: 21228 SE8-006

Applicant: Pfizer, Inc.

Trade/Generic Name: Detrol LA®

Indication: Overactive Bladder

Date of Submission: Oct. 14, 2003

Filing Date: Nov 25, 2003

User Fee Goal Date: Apr. 14, 2004

Project Manager: King

Medical Reviewer: Soule

Comments: This electronic NDA is fileable from a statistical perspective. In response to the Jan. 23, 2001 Written Request letter, the sponsor conducted additional pharmacological and clinical studies to support a pediatric exclusivity determination and proposed labeling changes. The two principal clinical studies submitted in this supplement are 583E-URO-0084-020 and DETAPE-0581-008. Both studies were randomized, double-blind, placebo-controlled, multicenter, multinational trials. The primary objective of each study was to compare the clinical efficacy of tolterodine PR 2 mg QD and placebo, as defined by the change in number of daytime incontinence episodes per week after 12 weeks of treatment, in children 5 to 10 years of age.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	Access to EDR data OK
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	Review issue

Reviewer: M. Welch

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this page is the manifestation of the electronic signature.

/s/

Mike Welch
12/2/03 02:05:45 PM
BIOMETRICS

K2.1A



K2.1A

N21228



N21228

NDA 21-228/S 006

**DETROL LA® (tolterodine tartrate)
Extended Release Capsules
Sponsor: Pfizer Pharmaceuticals**

*REC.
05/08/04
3:00PM*

**Submission of Pediatric Study Reports-
Pediatric Exclusivity Determination Requested**

Submission Date: October 10, 2003

Receipt Date: October 14, 2003

Pediatric Exclusivity Board Review: January 5, 2004

PDUFA Exclusivity Granted: January 6, 2004

PDUFA Date for Efficacy Approval Action: April 14, 2004

REVIEW TEAM:

Medical Team Leader: George Benson, M.D.

Medical Officer: Lisa Soule, M.D.

Clinical Pharmacology Team Leader: Ameeta Parekh, Ph.D.

Clinical Pharmacology Reviewer: DJ Chatterjee, Ph.D.

Regulatory Project Manager: Jean Makie, M.S., R.D.

Chief Regulatory Project Manager: Margaret Kober, R.Ph.

Volume 1 of 1

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Table of Contents

Volume 1

Project Management's Action Packet Checklist
User Fee Information
Action Letter
FDA Revised PI
FDA Revised PPI
FDA Revised Carton Labels
Sponsor Revised PI
Sponsor Proposed PI
Sponsor Revised PPI
Sponsor Proposed PPI
Sponsor Revised Carton Labels
Sponsor Proposed Carton Labels
Sponsor Container Labels
Other In Class Labeling
Foreign Labeling
DDMAC Review
Office of Drug Safety (ODS) Review
Application Integrity (AIP)
Post-Marketing Commitments
Special Programs
Public Communications
Federal Register Notices
Patent Information
Exclusivity Summary
Debarment Certification
Financial Disclosure Information
FDA Written Request/Written Request Amendments
FDA Correspondences/Memoranda/Faxes
Minutes of Meetings and Teleconferences
Advisory Committee Meeting
Office Director Memo
Division Director Memo
Group Leader Memo
Clinical Reviews/Memos
Safety Update Review(s)
Pediatric Page/Pediatric Exclusivity
Administrative Review
Statistical Review
Biopharmaceutical Review(s)
Controlled Substance Staff Review(s)

Micro Efficacy Review
Clinical Inspection Review Summary (DSI)
CMC Review(s)
Drug Master File (DMF)
Environmental Assessment
Micro Sterility Review(s)
Facilities Inspection (EES)
Methods Validation
Pharm/Tox Review(s)
Nonclinical Inspection Review Summary
Statistical Review(s) of Carcinogenicity Studies
CAC/ECAC Report

NOA 21-228

ACSM ~~FORM~~ CHECK LIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-228	Efficacy Supplement Type SE- 8	Supplement Number: 006	<i>Drift</i>
Drug: Detrol LA (tolterodine tartrate extended release capsules)		Applicant: Pfizer Inc.	
RPM: Jean Makie, M.S., R.D.		HFD-580	Phone # 301-827-4620
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:			
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
• Chem class (NDAs only)		IS	
• Other (e.g., orphan, OTC)		N/A	
❖ User Fee Goal Dates		April 14, 2004	
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	
❖ User Fee Information			
• User Fee		<input checked="" type="checkbox"/> Paid	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)		N/A	
• OC clearance for approval		N/A	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified	
❖ Patent			
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified	

Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary 	Pediatric exclusivity granted 1/5/04
<ul style="list-style-type: none"> Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification! 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	X
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA (X) AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	No previous actions for S 006
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	<input type="checkbox"/> Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release <input type="checkbox"/> Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	X
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	X
<ul style="list-style-type: none"> Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings) 	X
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	Ditropan, Ditropan XL, Oxytrol
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A No new carton/container label changes proposed by sponsor
<ul style="list-style-type: none"> Applicant proposed 	N/A
<ul style="list-style-type: none"> Reviews 	N/A
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	N/A
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	N/A
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	N/A
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	N/A
<ul style="list-style-type: none"> Other 	N/A

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	X
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	X (see clinical review)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	X
❖ Biopharmaceutical review(s) (indicate date for each review)	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A – not requested as studies did not demonstrate efficacy in pediatric population
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	X
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	N/A – S006 contains no new CMC information
• Review & FONSI (indicate date of review)	N/A – S006 contains no new CMC information
• Review & Environmental Impact Statement (indicate date of each review)	N/A – S006 contains no new CMC information
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	<input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation N/A – S006 contains no new CMC information
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested N/A – S006 contains no new CMC information
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	N/A – S006 contains no new pharm/tox information
❖ Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Sponsor Container Labels

Not applicable: this application does not propose changes to existing container labeling.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: March 1, 2004
From: Corrinne Kulick, DDMAC
To: Jean King, DRUDP
Re: Detrol LA (tolterodine tartrate extended release capsules)
NDA 21-228

Comments based on draft supplemental labeling submitted by Pharmacia & Upjohn Company OCT-2003.

DDMAC reviewed the pediatric supplemental labeling for Detrol LA (tolterodine tartrate extended release capsules) and offers the following 3 comments.

1. DDMAC recommends deletion of discussion of the pediatric studies in the Pharmacokinetics in Special Populations, Clinical Studies, and Adverse Reactions sections of the PI in order to avoid an implied effectiveness in the pediatric patient population that has not been demonstrated.
2. DDMAC recommends inclusion of the important safety information from these clinical studies in the Precautions-Pediatric Use section only, if clinically relevant, and including a prominent and concise statement about Detrol LA's ineffectiveness in this patient population. For example, "The effectiveness of Detrol LA in children has not been demonstrated."
3. Can the safety information in the Precautions-Pediatric Use section be qualified, i.e., "The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA compared to patients receiving placebo but all events were mild or moderate in severity. Typical anticholinergic effects (e.g., dry mouth, constipation) were seen at lower rates in pediatric patients than were observed in adults." Terms such as "higher," "mild or moderate," and "lower" are vague and require context. This information would be useful to the reader.

Thank you for requesting comments from DDMAC.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Post-Marketing Commitments

Not applicable to this application.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021228

NAME OF APPLICANT / NDA HOLDER

Pharmacia and Upjohn

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Detrol LA

ACTIVE INGREDIENT(S)

Tolterodine tartrate

STRENGTH(S)

2.0 mgs.

4.0 mgs.

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,382,600

b. Issue Date of Patent

01/17/1995

c. Expiration Date of Patent

01/17/2012

d. Name of Patent Owner

Pharmacia AB

Address (of Patent Owner)

SE - 112 87

City/State

Stockholm, Sweden

ZIP Code

FAX Number (if available)

(468) 695-4278

Telephone Number

(468) 695-8000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

 Craig M. Bell

Address (of agent or representative named in 1.e.)

Pfizer Inc.
150 East 42nd Street

City/State

New York, N.Y.

ZIP Code

10017

FAX Number (if available)

(212) 573-1939

Telephone Number

(212) 733-8791

E-Mail Address (if available)

Craig.M.Bell@Pfizer.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Craig M. Bell

9/4/03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Craig M. Bell

Address

Pfizer Inc.
150 East 42nd Street

City/State

New York, N.Y.

ZIP Code

10017

Telephone Number

(212) 733-8791

FAX Number (if available)

(212) 573-1939

E-Mail Address (if available)

Craig.M.Bell@Pfizer.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/dahtm/dahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021228

NAME OF APPLICANT / NDA HOLDER

Pharmacia and Upjohn

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Detrol LA

ACTIVE INGREDIENT(S)

Tolterodine tartrate

STRENGTH(S)

2.0 mgs.

4.0 mgs.

DOSAGE FORM

Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,559,269

b. Issue Date of Patent

09/24/1996

c. Expiration Date of Patent

11/05/2013

d. Name of Patent Owner

Pharmacia AB

Address (of Patent Owner)

SE - 112 87

City/State

Stockholm, Sweden

ZIP Code

FAX Number (if available)

(468) 695-4278

Telephone Number

(468) 695-8000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

 Craig M. Bell

Address (of agent or representative named in 1.e.)

Pfizer Inc.
150 East 42nd Street

City/State

New York, N.Y.

ZIP Code

10017

FAX Number (if available)

(212) 573-1939

Telephone Number

(212) 733-8791

E-Mail Address (if available)

Craig.M.Bell@Pfizer.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Claim Number (as listed in the patent) 14 and 15 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
 Method of treating acetylcholine - mediated disorders
 Method of treating urinary incontinence

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Craig M. Bell

Date Signed

9/4/03

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Craig M. Bell	
Address Pfizer Inc. 150 East 42nd Street	City/State New York, N.Y.
ZIP Code 10017	Telephone Number (212) 733-8791
FAX Number (if available) (212) 573-1939	E-Mail Address (if available) Craig.M. Bell@Pfizer.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

I. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

EXCLUSIVITY SUMMARY for NDA # NDA 21-228/S006

Trade Name Requested Detrol LA

Generic Name tolterodine tartrate extended release capsules

Applicant Name Pfizer Inc. HFD- 580

Approval Date April 14, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

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

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

This submission, which was received on October 14, 2003, contains pediatric efficacy studies, including PK and proposed labeling (for NDA 21-228 only; proposed labeling was not submitted to NDA 20-771), and also serves as the sponsor's submission of pediatric study reports and their request for determination of pediatric exclusivity. The submission does not contain any new CMC or pharmacology/toxicology information. At the same time as this submission, the sponsor also filed a general correspondence letter to NDA 20-771 to reference their NDA 21-228 submission of pediatric study results to satisfy the Written Request for Pediatric Studies issued by DRUDP jointly to both NDAs.

The Pediatric Exclusivity Board met on January 5, 2004 and determined that the sponsor should be granted an additional 6-month exclusivity for both NDA 21-228 and NDA 20-771.

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 /___/

NDA 21-228/S006 Detrol LA

tolterodine tartrate extended release capsules, 2 and 4 mg

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

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

d) Did the applicant request exclusivity?

YES / / NO / /

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

6-month pediatric exclusivity

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

YES / / NO / /

**On 1/5/04

* The indicated disease/condition (Treatment of the involuntary loss or leakage of urine in women during physical exertion or activities such as laughing, coughing, sneezing, lifting, exercising- stress urinary incontinence(SUI))does not exist in children.

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

NDA 21-228/S006 Detrol LA

tolterodine tartrate extended release capsules, 2 and 4 mg

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)

*****PART II is NOT APPLICABLE to this supplemental 006 application which seeks only 6-month pediatric exclusivity.**

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

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

an already approved active moiety.

YES /___/ NO /___/

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

NDA # _____

NDA # _____

2. Combination product. N/A

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

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

***PART III is NOT APPLICABLE to this supplemental 006 application which seeks only 6-month pediatric exclusivity.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

tolterodine tartrate extended release capsules, 2 and 4 mg

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

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

YES / ___ / NO / ___ /

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the

tolterodine tartrate extended release capsules, 2 and 4 mg

applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

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

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

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

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

Investigation #1 YES /___/ NO /___/

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation # 3, Study # _____

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

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

Investigation #1

!

!

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

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

	!	
	!	
	!	
Investigation #2	!	
IND # _____ YES /___/	!	NO /___/ Explain:
	!	
	!	
	!	
Investigation #3	!	
IND # _____ YES /_ _/	!	NO /___/ Explain:
	!	
	!	
	!	
Investigation #4	!	
IND # _____ YES /_ _/	!	NO /___/ Explain:
	!	
	!	
	!	
Investigation #5	!	
IND # _____ YES /_ _/	!	NO /___/ Explain:
	!	
	!	
	!	

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the

NDA 21-228/S006 Detrol LA

tolterodine tartrate extended release capsules, 2 and 4 mg

sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

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

YES /___/ NO /___/

If yes, explain: _____

{See appended electronic signature page}

Jean King, M.S., R.D.
Signature of Preparer

Date

Title: Project Manager

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

{See appended electronic signature page}

Date

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

DEBARMENT CERTIFICATION

The Clinical Research Unit of Pharmacia certifies that we have not used in any capacity the services of any debarred person in connection with DETROL LA™ (Tolterodine Tartrate), Pediatric Exclusivity Supplement, NDA # 21-228.



Ferdinand Massari, MD
Group Vice President
Clinical Research

30 August 2013
Date

DEBARMENT CERTIFICATION

The Clinical Pharmacology Research Unit of Pharmacia certifies that we have not used in any capacity the services of any debarred person in connection with DETROL LA™ (Tolterodine Tartrate), Pediatric Exclusivity Supplement, NDA # 21-228.



Paul Glue, MD, PhD
Executive Director, Clinical Sciences
Pfizer, Inc
235 East 42nd St, New York, NY 10017



Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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 certify 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 lists	

- (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	FERDINAND E. MASSARI	TITLE	Vice President	
FIRM / ORGANIZATION	Pfizer			
SIGNATURE	Ferdinand E. Massari		DATE	31 July 2003

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 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

Product: TOLTERODINE

Protocol: 583E-URO-0581-001

Protocol Title: Phase III, open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine liquid in children w/detrusor hyperreflexia 1 month to 4 yrs of age.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Aranda	Jacob V		Pharmacia	Received	16-Aug-01
Aranda			Pharmacia	Received	15-Aug-01
Aranda			Pharmacia	Received	12-Feb-02
Aranda			Pharmacia	Received	16-Aug-01
Aranda			Pharmacia	Received	8-Jan-02
Barone	Joseph G		Pharmacia	Received	19-Nov-01
Barone			Pharmacia	Received	8-Nov-01
Barone			Pharmacia	Received	10-Jul-02
Bauer	Stuart		Pharmacia	Received	6-Sep-01
Bauer			Pharmacia	Received	6-Sep-01
Blowey	Douglas		Pharmacia	Received	2-Aug-01
Blowey			Pharmacia	Received	21-Aug-01
Blowey			Pharmacia	Received	21-Aug-01
Blowey			Pharmacia	Received	2-Aug-01
Blowey			Pharmacia	Received	14-Feb-02
Blowey			Pharmacia	Received	22-Feb-02
Blowey			Pharmacia	Received	18-Feb-02
Blowey			Pharmacia	Received	21-Aug-01
Blowey			Pharmacia	Received	22-Aug-01
Blowey			Pharmacia	Received	21-Aug-01

Product: TOLTERODINE

Protocol: 583E-URO-0581-001

Protocol Title: Phase III, open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine liquid in children w/detrusor hyperreflexia 1 month to 4 yrs of age.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Bundrick	William Stuart		Pharmacia	Received	9-Aug-01
Bundrick			Pharmacia	Received	10-Aug-01
Bundrick			Pharmacia	Received	13-Aug-01
Bundrick			Pharmacia	Received	10-Aug-01
Bundrick			Pharmacia	Received	10-Aug-01
Bundrick			Pharmacia	Received	22-Aug-01
Bundrick			Pharmacia	Received	20-Aug-01
Bundrick			Pharmacia	Received	10-Aug-01
Bundrick			Pharmacia	Received	13-Aug-01
Bundrick			Pharmacia	Received	13-Aug-01
Bundrick			Pharmacia	Received	9-Aug-01
Bundrick			Pharmacia	Received	13-Aug-01
Bundrick			Pharmacia	Received	10-Aug-01
Bundrick			Pharmacia	Received	13-Aug-01
Cendron	Mark		Pharmacia	Received	7-Aug-01
Cendron			Pharmacia	Received	7-Aug-01
Cendron			Pharmacia	Received	6-Aug-01
Decter	Ross		Pharmacia	Received	13-Apr-02
Decter			Pharmacia	Received	12-Apr-02
Decter			Pharmacia	Received	16-Aug-02
Ewalt	Pamela		Pharmacia	Received	24-Jun-02
Ewalt			Pharmacia	Received	26-Jun-02
Jacoby	Karny		Pharmacia	Received	3-Aug-01
Jacoby			Pharmacia	Received	9-Aug-01
Jacoby			Pharmacia	Received	13-Aug-01

Product: TOLTERODINE

Protocol: 583E-URO-0581-001

Protocol Title: Phase III, open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine liquid in children with urinary hyperreflexia 1 month to 4 yrs of age.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Kogan	Barry A		Pharmacia	Received	2-Aug-01
Kogan			Pharmacia	Received	2-Aug-01
Kogan			Pharmacia	Received	13-Mar-02
Kogan			Pharmacia	Received	6-Aug-01
Minevich	Eugene A		Pharmacia	Received	23-Aug-01
Minevich			Pharmacia	Received	25-Sep-02
Minevich			Pharmacia	Received	21-Aug-01
Minevich			Pharmacia	Received	21-Aug-01
Minevich			Pharmacia	Received	26-Nov-01
Minevich			Pharmacia	Received	23-Aug-01
Minevich			Pharmacia	Received	21-Aug-01
Packer	Michael G		Pharmacia	Received	26-Mar-02
Packer			Pharmacia	Received	18-Mar-02
Packer			Pharmacia	Received	15-Mar-02
Packer			Pharmacia	Received	15-Mar-02
Reddy	Pramod		Pharmacia	Received	10-Oct-01
Reddy			Pharmacia	Received	29-Aug-02
Reddy			Pharmacia	Received	29-Aug-02
Reddy			Pharmacia	Received	1-Oct-01
Reddy			Pharmacia	Received	1-Oct-01
Reddy			Pharmacia	Received	2-Oct-01
Reddy			Pharmacia	Received	1-Oct-01
Ritchey	Michael L		Pharmacia	Received	17-Aug-01
Ritchey			Pharmacia	Received	17-Aug-01
Voigt	Roger W		Pharmacia	Received	7-Sep-01
Voigt			Pharmacia	Received	9-Aug-01

Product: TOLTERODINE Protocol: 583E-URO-0581-002 Protocol Title: Phase III, open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine liquid in children w/detrusor hyperreflexia 5 to 10 years of age.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Candron Candron Candron	Mark		Pharmacia Pharmacia Pharmacia	Received Received Received	7-Aug-01 7-Aug-01 6-Aug-01
Decter Decter Decter	Ross		Pharmacia Pharmacia Pharmacia	Received Received Received	13-Apr-02 16-Aug-02 12-Apr-02
Ewalt Ewalt	David Harris		Pharmacia Pharmacia	Received Received	24-Jun-02 26-Jun-02
Jacoby Jacoby Jacoby	Karny		Pharmacia Pharmacia Pharmacia	Received Received Received	3-Aug-01 13-Aug-01 9-Aug-01
Kogan Kogan Kogan Kogan	Barry A		Pharmacia Pharmacia Pharmacia Pharmacia	Received Received Received Received	2-Aug-01 2-Aug-01 13-Mar-02 6-Aug-01
Minevich Minevich Minevich Minevich Minevich Minevich Minevich	Eugene A		Pharmacia Pharmacia Pharmacia Pharmacia Pharmacia Pharmacia Pharmacia	Received Received Received Received Received Received Received	23-Aug-01 25-Sep-02 26-Nov-01 21-Aug-01 21-Aug-01 23-Aug-01 21-Aug-01

Product: TOLTERODINE Protocol: 583E-URO-0581-002 Protocol Title: Phase III, open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine liquid in children w/detrusor hyperreflexia 5 to 10 years of age.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Packer	Michael G		Pharmacia	Received	26-Mar-02
Packer			Pharmacia	Received	18-Mar-02
Packer			Pharmacia	Received	15-Mar-02
Packer			Pharmacia	Received	18-Mar-02
Reddy	Pramod		Pharmacia	Received	10-Oct-01
Reddy			Pharmacia	Received	3-Oct-01
Reddy			Pharmacia	Received	29-Aug-02
Reddy			Pharmacia	Received	3-Oct-01
Reddy			Pharmacia	Received	29-Aug-02
Reddy			Pharmacia	Received	3-Oct-01
Reddy			Pharmacia	Received	3-Oct-01
Ritchey	Michael L		Pharmacia	Received	13-Nov-01
Ritchey			Pharmacia	Received	17-Aug-01
Voigt		Roger W	Pharmacia	Received	18-Aug-01
Voigt			Pharmacia	Received	7-Aug-01

Product: TOLTERODINE Protocol: 583E-URO-0581-003 Protocol Title: Phase III open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine PR capsules children with detrusor hyperreflexia 11 to 15 years of age.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Aranda	Jacob		Pharmacia	Received	16-Aug-01
Aranda	Jacob		Pharmacia	Received	15-Aug-01
Aranda	Jacob		Pharmacia	Received	12-Feb-02
Aranda	Jacob		Pharmacia	Received	16-Aug-01
Aranda	Jacob		Pharmacia	Received	8-Jan-02
Bauer	Stuart		Pharmacia	Received	6-Sep-01
Bauer	Stuart		Pharmacia	Received	6-Sep-01
Bundrick	W. Stewart		Pharmacia	Received	9-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	20-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	10-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	22-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	10-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	10-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	10-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	13-Aug-01
Bundrick	W. Stewart		Pharmacia	Received	9-Aug-01
Cendron	Marc	Marc Cendron, MD	Pharmacia	Received	7-Aug-01
Cendron	Marc	Marc Cendron, MD	Pharmacia	Received	7-Aug-01
Cendron	Marc	Marc Cendron, MD	Pharmacia	Received	6-Aug-01

Product: TOLTERODINE Protocol: 583E-URO-0581-003 Protocol Title: Phase III open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine PR capsules children with detrusor hyperreflexia 11 to 15 years of age.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Decter	Ross		Pharmacia	Received	13-Apr-02
Decter	Ross		Pharmacia	Received	16-Aug-02
Decter	Ross		Pharmacia	Received	12-Apr-02
Ewalt	David		Pharmacia	Received	24-Jun-02
Ewalt	David		Pharmacia	Received	26-Jun-02
Jacoby	Karny		Pharmacia	Received	3-Aug-01
Jacoby	Karny		Pharmacia	Received	13-Aug-01
Jacoby	Karny		Pharmacia	Received	9-Aug-01
Kogan	Barry		Pharmacia	Received	2-Aug-01
Kogan	Barry		Pharmacia	Received	2-Aug-01
Kogan	Barry		Pharmacia	Received	13-Mar-02
Kogan	Barry		Pharmacia	Received	6-Aug-01
Minevich	Eugene		Pharmacia	Received	23-Aug-01
Minevich	Eugene		Pharmacia	Received	25-Sep-02
Minevich	Eugene		Pharmacia	Received	26-Nov-01
Minevich	Eugene		Pharmacia	Received	21-Aug-01
Minevich	Eugene		Pharmacia	Received	21-Aug-01
Minevich	Eugene		Pharmacia	Received	23-Aug-01
Minevich	Eugene		Pharmacia	Received	21-Aug-01
Minevich	Eugene		Pharmacia	Received	21-Aug-01

Product: TOLTERODINE Protocol: 583E-URO-0581-003 Protocol Title: Phase I/II open label, dose-escalating pharmacokinetic pharmacodynamic (urodynamic) and clinical effect, and safety study of tolterodine PR capsules children with detrusor hyperreflexia 11 to 15 years of age.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Packer	Michael		Pharmacia	Received	26-Mar-02
Packer	Michael		Pharmacia	Received	18-Mar-02
Packer	Michael		Pharmacia	Received	15-Mar-02
Packer	Michael		Pharmacia	Received	18-Mar-02
Reddy	Pramod		Pharmacia	Received	10-Oct-01
Reddy	Pramod		Pharmacia	Received	3-Oct-01
Reddy	Pramod		Pharmacia	Received	29-Aug-02
Reddy	Pramod		Pharmacia	Received	2-Oct-01
Reddy	Pramod		Pharmacia	Received	29-Aug-02
Reddy	Pramod		Pharmacia	Received	3-Oct-01
Reddy	Pramod		Pharmacia	Received	3-Oct-01
Ritchey	Michael		Pharmacia	Received	17-Aug-01
Ritchey	Michael		Pharmacia	Received	17-Aug-01
Scherz	Hal		Pharmacia	Received	17-Jul-02
Scherz	Hal		Pharmacia	Received	16-Jul-02
Scherz	Hal		Pharmacia	Received	11-Jul-02
Scherz	Hal		Pharmacia	Received	19-Aug-02
Scherz	Hal		Pharmacia	Received	12-Jul-02
Voigt	Roger		Pharmacia	Received	15-Aug-01
Voigt	Roger		Pharmacia	Received	7-Sep-01

Product: TOLTERODINE

Protocol: DETAPE-0581-008

Protocol Title: Phase III randomized, double blind, multicenter and multinational study to determine efficacy and safety of Tolterodine prolonged release capsules in children 5 to 10 years of age w/ symptoms of urge urinary incontinence suggestive of detrusor instability.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Allen	Robert		Pharmacia	Received	6-Feb-02
Allen		Received	Pharmacia	Received	7-Feb-02
Allen			Pharmacia	Received	6-Feb-02
Allen			Pharmacia	Received	7-Feb-02
Allen			Pharmacia	Received	8-Feb-02
Angel	Carlos		Pharmacia	Received	18-Apr-02
Angel			Pharmacia	Received	3-Jul-02
Angel			Pharmacia	Received	17-Apr-02
Bridges	Peter		Pharmacia	Received	28-Feb-02
Bridges			Pharmacia	Received	26-Mar-02
Bridges			Pharmacia	Received	26-Feb-02
Bundrick	W. Stewart		Pharmacia	Received	19-Feb-02
Bundrick			Pharmacia	Received	18-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02
Bundrick			Pharmacia	Received	25-Feb-02
Bundrick			Pharmacia	Received	20-Feb-02
Bundrick			Pharmacia	Received	18-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02
Bundrick			Pharmacia	Received	18-Feb-02
Bundrick			Pharmacia	Received	18-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02
Bundrick			Pharmacia	Received	19-Feb-02
Bundrick			Pharmacia	Received	19-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02
Bundrick			Pharmacia	Received	14-Feb-02

Product: TOLTERODINE

Protocol: DETAPE-0581-008

Protocol Title: Phase III randomized, double blind, multicenter and multinational study to determine efficacy and safety of Tolterodine prolonged release capsules in children 5 to 10 years of age w/ symptoms of urge urinary incontinence suggestive of detrusor instability.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Caldamone	Anthony		Pharmacia	Received	13-Feb-02
Cooper	Christopher		Pharmacia	Received	1-Mar-02
Dectar	Ross		Pharmacia	Received	13-Apr-02
			Pharmacia	Received	12-Apr-02
Docimo	Steven		Pharmacia	Received	19-Feb-02
Docimo			Pharmacia	Received	20-Feb-02
Docimo			Pharmacia	Received	20-Feb-02
Ellsworth	Pamela		Pharmacia	Received	14-Feb-02
Erhard	Michael		Pharmacia	Received	11-Feb-02
Erhard			Pharmacia	Received	24-Apr-02
Erhard			Pharmacia	Received	23-Apr-02
Erhard			Pharmacia	Received	8-May-02
Forrest	John		Pharmacia	Received	14-Mar-02
Forrest			Pharmacia	Received	28-Feb-02
Forrest			Pharmacia	Received	21-Mar-02
Forrest			Pharmacia	Received	25-Mar-02
Hassman	David		Pharmacia	Received	14-Feb-02
Hassman			Pharmacia	Received	1-Apr-02
Hassman			Pharmacia	Received	14-Feb-02
Hassman			Pharmacia	Received	14-Feb-02
Hassman			Pharmacia	Received	1-Apr-02
Hassman			Pharmacia	Received	2-Apr-02
Hassman			Pharmacia	Received	18-Feb-02
Hassman			Pharmacia	Received	18-Feb-02

Product: TOLTERODINE

Protocol: DETAPE-0581-008

Protocol Title: Phase III randomized, double blind, multicenter and multinational study to determine efficacy and safety of Tolterodine prolonged release capsules in children 5 to 10 years of age w/ symptoms of urge urinary incontinence suggestive of detrusor instability.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Jacoby	Karny		Pharmacia	Received	13-Mar-02
Jacoby			Pharmacia	Received	14-Mar-02
Jacoby			Pharmacia	Received	14-Mar-02
Kogan	Barry		Pharmacia	Received	20-Feb-02
Kogan			Pharmacia	Received	19-Feb-02
Kogan			Pharmacia	Received	21-Feb-02
Kogan			Pharmacia	Received	15-Mar-02
Lacy	Sushil		Pharmacia	Received	7-Feb-02
Lacy			Pharmacia	Received	8-Feb-02
Lacy			Pharmacia	Received	11-Feb-02
Lacy			Pharmacia	Received	8-Feb-02
Lacy			Pharmacia	Received	4-Mar-02
Lacy			Pharmacia	Received	8-Feb-02
Lacy			Pharmacia	Received	12-Feb-02
Lacy			Pharmacia	Received	8-Feb-02
Lindgren	Bruce		Pharmacia	Received	18-Mar-02
Lindgren			Pharmacia	Received	10-Mar-02
Lowe	Phillip		Pharmacia	Received	15-Feb-02
Middleton	George		Pharmacia	Received	15-Feb-02
Middleton			Pharmacia	Received	14-Feb-02
Middleton			Pharmacia	Received	22-Feb-02
Minevich	Eugene		Pharmacia	Received	15-Feb-02
Minevich			Pharmacia	Received	14-Feb-02
Minevich			Pharmacia	Received	11-Feb-02
Minevich			Pharmacia	Received	6-Mar-02

Product: TOLTERODINE Protocol: DETAPE-0581-008 Protocol Title: Phase III randomized, double blind, multicenter and multinational study to determine efficacy and safety of Tolterodine prolonged release capsules in children 5 to 10 years of age w/ symptoms of urge urinary incontinence suggestive of detrusor instability.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Palmer	Lane		Pharmacia	Received	14-Feb-02
Palmer			Pharmacia	Received	14-Feb-02
Palmer			Pharmacia	Received	14-Feb-02
Palmer			Pharmacia	Received	14-Feb-02
Rich	Mark		Pharmacia	Received	26-Feb-02
Rich			Pharmacia	Received	22-Feb-02
Rich			Pharmacia	Received	25-Feb-02
Rich			Pharmacia	Received	6-Mar-02
Rich			Pharmacia	Received	22-Feb-02
Rosenberg	Steven		Pharmacia	Received	8-Feb-02
Rosenberg			Pharmacia	Received	7-Feb-02
Rosenberg			Pharmacia	Received	7-Feb-02
Rosenberg			Pharmacia	Received	8-Feb-02
Rosenberg			Pharmacia	Received	8-Feb-02
Rosenberg			Pharmacia	Received	15-Feb-02
Rosenberg			Pharmacia	Received	15-Feb-02
Scherz	Hal		Pharmacia	Received	3-Apr-02
Scherz			Pharmacia	Received	6-May-02
Scherz			Pharmacia	Received	29-Mar-02
Scherz			Pharmacia	Received	3-Apr-02
Scherz			Pharmacia	Received	2-Apr-02
Slaughenhaupt	Bruce		Pharmacia	Received	28-Mar-02
			Pharmacia	Received	28-May-02
			Pharmacia	Received	28-May-02

Product: TOLTERODINE

Protocol: DETAPE-0581-008

Protocol Title: Phase III randomized, double blind, multicenter and multinational study to determine efficacy and safety of Tolterodine prolonged release capsules in children 5 to 10 years of age w/ symptoms of urge urinary incontinence suggestive of detrusor instability.

Inv Last Name	Inv First Name	Sub Investigator Name	Discosure Type	Discosure Status	Signature Date
Teague Teague Teague	Julius		Pharmacia Pharmacia Pharmacia	Received Received Received	21-Feb-02 18-Mar-02 18-Mar-02
Tenney Tenney	Jackie		Pharmacia Pharmacia	Received Received	20-Feb-02 22-Feb-02
Thomalia	James		Pharmacia	Received	12-Feb-02

Product: TOLTERODINE

Protocol: 583E-URO-0084-020

Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Jochum Jochum	Bernhard, MD		Pharmacia Pharmacia	received received	12-Dec-00 12-Dec-00
Marberger Marberger	Johann, MD		Pharmacia	received	12-Feb-01 12-Feb-01
Radmayr	Christian, MD, Prof.		Pharmacia	received	05-Jan-01
Riccabona Riccabona	Marcus, MD		Pharmacia Pharmacia	received received	12-Dec-00 12-Dec-00

Product: TOLTERODINE Protocol: 583E-URO-0084-020 Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Belgium					
Bael	An, MD		Pharmacia	received	05-Dec-00
Bogaert	Guy, MD, Prof.		Pharmacia	received	03-May-01
Hoebeke	Piet, MD, Prof		Pharmacia	received	04-Dec-00
Hoebeke			Pharmacia	received	04-Dec-00
Schurmans	Thierry, MD		Pharmacia	received	15-Dec-00
Schurmans			Pharmacia	received	15-Dec-00
Sorber	Marc, MD		Pharmacia	received	11-Dec-00
Van De Walle	Johan, MD, Prof		Pharmacia	received	04-Dec-00
Van De Walle			Pharmacia	received	04-Dec-00
Van De Walle			Pharmacia	received	04-Dec-00
Van Dyck	Maria, MD		Pharmacia	received	23-Jan-01
Van Hoeck	Koen; MD		Pharmacia	received	19-Dec-00

Product: TOLTERODINE Protocol: 583E-URO-0084-020 Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Djurhuus	Jens C., MD, Prof		Pharmacia	received	04-Sep-00
Djurhuus			Pharmacia	received	05-Sep-00
Djurhuus			Pharmacia	received	13-Sep-00
Djurhuus			Pharmacia	received	02-Feb-01
Hansen	Anita, MD		Pharmacia	received	16-Aug-00
Hansen			Pharmacia	received	17-Aug-00
Thorup	Jørgen, Ph.D.		Pharmacia	received	02-Oct-00
Germany					
Hoang-Böhm	Jeannette, MD		Pharmacia	received	12-Dec-00
Hoang-Böhm			Pharmacia	received	12-Dec-00
Marschall-Kehrel	Daniela, MD		Pharmacia	received	08-Dec-00
Schumacher	Stefan MD		Pharmacia	received	12-Jan-01
Schumacher			Pharmacia	received	12-Jan-01

Product: TOLTERODINE Protocol: 583E-URO-0084-020 Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.					
Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
HongKong					
Yeung Yeung	Chung Kwong, MD, Prof.		Pharmacia Pharmacia	received received	11-Apr-01 11-Apr-01
The Netherlands					
De Jong De Jong	T.P.V.M, MD		Pharmacia Pharmacia	received received	17-Jan-01 14-Mar-01
Feltz	W.F.J, PhD		Pharmacia	received	08-Dec-00
Froeling	F.M.J.A, MD		Pharmacia	received	29-Nov-00
Nijman Nijman	J.M, PhD		Pharmacia Pharmacia	received received	22-Dec-00 30-Nov-00
Van Capelle	J.W, MD		Pharmacia	received	11-Jan-01

Product: TOLTERODINE

Protocol: 583E-URO-0084-020

Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Bakke	August, MD, Prof		Pharmacia	received	25-Aug-00
Bangstad	Hans-Jacob, MD		Pharmacia	received	02-Jul-00
Bangstad	Elirik, MD, Prof.		Pharmacia	received	21-Aug-00
Monn	Jon, MD		Pharmacia	received	29-Aug-00
Sten-Jonsen			Pharmacia	received	
Sten-Jonsen			Pharmacia	received	
Russia					
Menovshikova	Lyudmila MD		Pharmacia	received	06-Feb-01
Romikh	V.V, MD		Pharmacia	received	12-Feb-01
Vishnevsky	Evgeny A., MD, Prof.		Pharmacia	received	06-Mar-01
Slovenia					
Trsinar	Bojan, MD, Prof.		Pharmacia	received	04-Dec-00
Trsinar			Pharmacia	received	04-Dec-00
Trsinar			Pharmacia	received	04-Dec-00
Sweden					
Läckgren	Göran, PhD		Pharmacia	received	04-Sep-00
Läckgren			Pharmacia	received	03-Dec-01
Linné	Tommy, PhD		Pharmacia	received	22-Feb-01

Product: TOLTERODINE

Protocol: 583E-URO-0084-020

Protocol Title: Clinical efficacy and safety of tolterodine prolonged release capsules 2 mg qd compared to placebo in children with symptoms of urinary urge incontinence suggestive of detrusor instability. A phase III randomized, double blind, multinational study.

Inv Last Name	Inv First Name	Sub Investigator Name	Disclosure Type	Disclosure Status	Signature Date
Agerwal	Sanjiv, MD		Pharmacia	received	12-Dec-00
Borzysowski Borzysowski	Malgorzata, MD		Pharmacia Pharmacia	received received	22-Aug-00 22-Aug-00
El-Radhi	A.S, MD		Pharmacia	received	30-Nov-00
Evans	Jonathan, MD		Pharmacia	received	05-Sep-00
Frank Frank	David, MD				30-Nov-00 24-Aug-00
Gough	David, MD				10-Jan-01
Malone	Padraid, MD				23-Aug-00
Parashar	Karan, MD				01-Feb-01
Preece	Phillip, MD				26-Sep-00
Rickwood Rickwood	A.M.K., MD				01-Dec-00 21-Aug-00

NDA 21-228/S006 Detrol LA

tolterodine tartrate extended release capsules, 2 and 4 mg

Controlled Substance Staff Review

Not applicable to this application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Micro Efficacy Review

Not applicable to this application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Microbiology Sterility Review

Not applicable to this application (microbiology review is not required for oral tablets).

NDA 21-228/S-006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Clinical Inspection Summary

Not applicable. No new inspection information was submitted in this supplemental application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Environmental Assessment

Not applicable. No new CMC information was submitted in this supplemental application.

**ENVIRONMENTAL ASSESSMENT
CLAIM FOR A CATEGORICAL EXCLUSION**

**Supplement to NDA # 21-228
For Pediatric Exclusivity**

Under the provisions of 21 CFR 25.31(b), action on an NDA is categorically excluded and, therefore, ordinarily does not require the preparation of an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The total planned production of Tolterodine Tartrate is estimated to be at levels where the aquatic concentration is estimated to be under a concentration of 1 part per billion. To the best knowledge of Pharmacia & Upjohn, the applicant is not aware of the existence of any extraordinary circumstances that would require the preparation of an Environmental Assessment. Also, Pharmacia & Upjohn does not have any information to indicate that Tolterodine Tartrate may be toxic to organisms in the environment at the expected levels of exposure. Pharmacia & Upjohn claims a categorical exclusion to the EA requirements in accordance with 21 CFR 25.31(b).

1. Date

August 11, 2003

2. Name of Applicant

Pharmacia & Upjohn*
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Contact: Richard T. Williams
Tel. (860) 441-6287

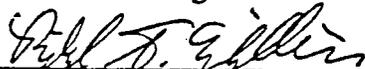
3. List of Preparers

Richard T. Williams, Ph.D.
Asst. Director, Environmental Sciences

Ph.D. in Microbiology with twenty- one years
in chemical fate and effect evaluations, EHS,
and regulatory compliance.

4. Certification

The undersigned certifies that the information presented is true, accurate, and complete to the best knowledge of Pharmacia & Upjohn.


Richard T. Williams, Ph.D.

20 August 2003
Date.

*Pharmacia & Upjohn is a wholly owned subsidiary of Pfizer Inc.

NDA 21-228/S006 Detrol LA

tolterodine tartrate extended release capsules, 2 and 4 mg

Facilities Inspection (EES)

Not applicable. No new CMC information was submitted in this supplemental application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Nonclinical Inspection Review Summary

Not applicable to this application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

Statistical Review(s) of Carcinogenicity Studies

Not applicable for this application.

NDA 21-228/S006 Detrol LA
tolterodine tartrate extended release capsules, 2 and 4 mg

CAC/ECAC Report

Not applicable for this application.