CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-771

ADMINISTRATIVE DOCUMENTS

Division Director NDA REVIEW

MAR 16 1998

NDA: 20-771 Detrol (Tolterodine) tablets 1 and 2 mg strength

Sponsor: Pharmacia and Upjohn

Submission date: March 24, 1997

Date of Review: March 16, 1998

This application presents background, protocols, and results from several clinical and pharmacokinetics studies in support of tolterodine (1 and 2mg orally, bid), an antimuscarinic agent, for the requested indication of the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Chemistry and manufacturing controls information as well as an appropriate pharmacology package are also included.

A synopsis will be made here of the reviews of this application as well as a recommendation to the Office of Drug Evaluation II of approval for the indication of "treatment of bladder overactivity with symptoms of urinary frequency, urgency or urge incontinence".

Physiology and Background

As noted in the Medical Officer review: detrusor muscle contractions are mainly mediated through cholinergic, muscarinic receptor stimulation. Inappropriate detrusor contraction can lead to a sensation of urgency. Increased urgency can lead to urinary frequency, nocturia and "urge incontinence" (if the urge to void cannot be resisted). The main pharmacologic therapy for this condition is directed at reducing the activity of the detrusor muscle with antimuscarinic agents.

Oxybutynin, an anti-cholinergic, anti-muscarinic agent is currently the most commonly prescribed therapy for urge incontinence. As would be expected from an anti-cholinergic agent, side effects such as dry mouth, reduced visual accommodation and constipation are common (often leading to discontinuation of drug therapy). This sponsor asserts that tolterodine is a competitive muscarinic antagonist that exhibits selective antimuscarinic activity for bladder receptors as compared to receptors in the salivary gland. Because of this "selectivity" the sponsor anticipated effectiveness similar to oxybutynin with an improved side effect profile (especially as relates to symptoms of dry mouth).

Important in the consideration of the safety of this product is the consideration of terodiline, a close chemical structure cousin of tolterodine. Terolidine is a product that was once approved in Sweden for the indication of angina pectoris and later withdrawn from the market due to safety

reasons. This drug was found to have calcium channel blocking as well as other effects which increased the QT interval in humans which appeared to be associated with ventricular dysrhythmias including torsades de pointes. The marketing of terodiline was therefore halted. Because of the similarity of the two drugs, tolterodine was extensively tested for this association and none was found (see pharmacology, biopharmaceutics and medical officer safety reviews).

As discussed in the primary reviews, tolterodine is metabolized (with active metabolites) by the cytochrome P450 system. The issue of possible accumulation in "poor metabolizers", especially those taking concomitant medications which might block the alternative metabolic pathway, is discussed fully in the Clinical Pharmacology and Biopharmaceutics review. The clinical reviewer concludes that the adverse event profile comparison between "poor" and "extensive" metabolizers was not significant and the team recommends labeling to alert providers and users of the potential metabolism/accumulation issues.

Chemistry

Chemistry review issues were conveyed to the sponsor during the review process. Each were adequately addressed. Of note is the tradename change from the original proposal of to the revised name, "Detrol". Needed labeling changes have been made. After discussion between this Division and the Division of Drug Marketing, Advertising and Communications, a , initially proposed as part of the trade name, has been removed from the tradename logo but will remain as part of promotional materials (separate from the name).

Pharmacology/Toxicology

As per the pharmacology review, tolterodine has been adequately tested in mice, rats and dogs. Little to no organ toxicity (other than that expected due to the antimuscarinic pharmacodynamic effects) was produced by tolterodine. The analyses of non-human pharmacokinetics results as well as specific cardiac monitoring in the preclinical studies support the conclusion that there exists an adequate safety margin to support human safety for both the "poor" and "extensive" metabolizer.

Biopharmaceutics

The Office of Clinical Pharmacology and Biopharmaceutics has provided an extensive review of the issues of protein binding, metabolism, pharmacokinetics, special populations and drug interactions. Much of the safety concerns raised relate to the metabolism/elimination of tolterodine via hepatic metabolism and specifically through the catalytic activity of cytochrome P450 2D6 and 3A4. Cytochrome P450 2D6 is a genetically polymorphic enzyme that is absent in approximately 7% of Caucasians, 1% East Asians and 1% Black Americans.

In looking at the metabolism data it appears that in extensive metabolizers, tolterodine acid and dealkylated hydoxylated tolterodine are present. In poor metabolizers, only dealkylated tolterodine was found. These findings are consistent with the predicted metabolic pathways. The final conclusion on this issue by the biopharmaceutics reviewer is that, although a theoretical risk of increased exposure exists, there appears to be no accumulation of tolterodine or its dealkylated metabolite in extensive metabolizers and no accumulation of dealkylated tolterodine in poor metabolizers after multiple dosing of 2 mg bid.

From review of drug-drug interaction studies, and based on the known metabolic pathways, the reviewer cautions that care should be taken when co-administering cytochrome P450 3A4 inhibitors (such as ketoconazole) along with Detrol. The reviewer recommends a starting dose of 1 mg in subjects with hepatic insufficiency and subjects with such concomitant drug use.

In terms of safety concerns related to the close chemical structure to terodiline, ECG data were scrutinized in Phase II and III studies and showed no difference in QT interval changes in tolterodine versus placebo treated subjects. This data also revealed showed no ECG differences in poor versus extensive metabolizers of tolterodine.

After further discussion in an OCPB briefing on March 11, 1998, it was decided that the sponsor should perform (Phase 4) a multiple dose pharmacokinetics and pharmacodynamic study in patients with hepatic impairment to assess the potential for ECG changes. Such a study would be proposed to the IND and performed within one year of approval. This Phase 4 commitment was discussed and agreed with the sponsor on March 12, 1998.

Clinical/Statistical

Three placebo-controlled, 12-week studies (studies 008, 009 and 010), constitute the pivotal clinical trials contained in this submission and involved randomization of 886 subjects (478 to tolterodine) with "detrusor overactivity" or "detrusor instability". Two of the studies (008 and 010) also incorporated an active control--Oxybutynin. The Medical Officer review describes the inclusion/exclusion criteria as well as baseline characteristics of those entered.

Along with the "pivotal" efficacy studies presented, the sponsor presents a total safety data base of 1645 subjects who took tolterodine for 6 months and 812 with 12 months of drug exposure.

The primary endpoint stated for the central studies was the change in mean number of micturitions per 24 hours from baseline to end of study (12 weeks). Secondary endpoints included an analysis of changes in mean number of incontinence episodes per 24 hours and mean volume voided per micturition.

For the primary endpoint (number of micturitions), tolterodine proved superior to placebo in two of the three central studies (008 and 009). In terms of change in mean volume voided per micturition, tolterodine was superior to placebo in all three studies. In none of the studies was

tolterodine found to be superior to placebo for changes in mean number of incontinence episodes per 24 hours (although in each study tolterodine appeared to be more efficacious in this parameter, the difference did not reach statistical significance).

The sponsor submitted an analysis of pooled data for the three studies. The medical reviewer believes that the pooling is appropriate as the protocols of the studies were virtually identical. When the data from both the individual and pooled analyses are considered, superiority of tolterodine 1 and 2 mg over placebo with regard to change in mean number of incontinent episodes per 24 hours is demonstrated. The pooled data support the individual study findings of superiority in regards to micturition numbers and voided volume parameters.

The statisticians have debated the merits of the pooling of the data from these three trials. Although the protocols are similar, there is a question of whether the sponsor employed a reclassification of patients (based on change of dose group during the study) which weakens their statistical argument for support. The medical officer continues to believe that urgency, frequency and eventual urge incontinence exist as a continuum of symptoms and that this product, with its confirmed mechanism of action, is appropriate for approval for the complete spectrum of symptomatology.

It should be noted that in the phase 3 clinical studies no statistically significant efficacy or safety differences between tolterodine 1 and 2 mg were demonstrated. Some trends in the data indicate that tolterodine 2 mg is more active than tolterodine 1 mg.

In those studies where oxybutynin (5 mg tid) was used an active comparator, oxybutynin tended to demonstrate increased efficacy compared to tolterodine. In one of the central studies, oxybutynin was statistically significantly superior to tolterodine in increasing the volume voided per micturition--a measure of antimuscarinic effect on the bladder. As noted in the clinical review, it is likely that tolterodine, given in equi-potent doses (in terms of antimuscarinic effects) would have similar effects as oxybutynin. The trials presented in this application do not appear to compare equi-potent doses (in terms of both effectiveness and side effect profile) of the two products.

Safety information is extensively reviewed in the MO review dated March 10, 1998. Serious adverse events and deaths reported appeared to be related to underlying medical conditions, advanced age, etc.. None could be clearly attributed to tolterodine use.

The most commonly reported adverse event was dry mouth. The incidence of dry mouth tended to be higher in the tolterodine groups (24-50%) than in placebo groups (13-21%) and highest in the oxybutynin groups (69-86%). The incidence of other antimuscarinic side effects (constipation, abnormal accommodation, constipation and urinary retention) was low and did not clearly demonstrate an increase over background rates.

Although the annoying side effect of "dry mouth" appears to be less with tolterodine than with the active comparator, it is noted that the incidence remains significant and that these trials were not designed to confirm superiority of tolterodine over oxybutynin for this endpoint. If a claim for decreased side effects such as dry mouth is to be made, at least one trial to assess this endpoint (in an adequately designed study) would be needed. Such a design would likely include a validated scoring/index system with set recording times, a clear definition of the endpoint, an agreed upon clinically meaningful difference between therapies for the endpoint and a rigorous attempt to assure equi-potent doses amongst the products compared in the study. These criteria were not met in any of the studies presented in this application.

In terms of monitoring for cardiac safety, the data from the pivotal as well as long-term safety studies gave no indication that tolterodine precipitated cardiac events. In the analyses, tolterodine use was not associated with lengthened QT intervals, other ECG changes, arrhythmias or other clinical signs and symptoms of cardiac disease.

RECOMMENDATION:

As per the review team conclusions, approval is recommended. Labeling discussions have been productive and the Division supports the labeling as proposed in the March 12, 1998 submission. The Phase 4 commitment for has been incorporated into the action package.

3/16/98 /S/

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Products, HFD-580

cc:
archival
HFD-580
HFD-580\LRarick, DShaughnes, ADunson, LKammerman, BTaneja, ADorantes, GBarnette, AJordan, MRhee
HFD-102\JBilstad

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Group Leader's Memo

No Group Leader's memo will be prepared; comments will be provided in the Division Director Memo.

NDA 20-771
DETRUSITOL™ Tablets

XIII. PATENT INFORMATION

PATENT CERTIFICATION

1.	Active Ingredient	Tolterodine L-Tartrate
2.	Strength(s)	1 mg and 2 mg
3.	Trade Name	DETRUSITOL™ Tablets
4.	a. Dosage Form	Tablets
	b. Route of Administration	Oral
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	20-771
7.	NDA Approval Date	To be determined
8.	Exclusivity - Date first ANDA could be approved and length of exclusivity period.	Five (5) years after date of NDA approval.
9.	Applicable patent numbers and expiration date of each.	5,382,600 Expiration date-2012 Claims cover 3,3-diphenylpropylamines, including tolterodine, and pharmaceutical compositions comprising them.

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

Kerstin Franzén
Director of Regulatory Affairs
Pharmacia & Upjohn AB
Sweden.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A/BLA # 20-771 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-580 Trade and generic names/dosage form: DETROL Tablets (tolterodine tablets) Action: (AP) AE NA

Applicant Pharmacia & Upjohn Therapeutic Class 15 / MUSCARINIC RECEPTOR ANTAGONIST

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title 1/5/98 Date

cc: Orig (NDA) BLA # 20-771
HFD-580 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

DEBARMENT CERTIFICATION

Detrol™
tolterodine tartrate tablets
(NDA 20-771)

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

Edward L. Patt

2/13/98

Ed L. Patt
Manager
Regulatory Compliance

Date

NDA 20-771
DETROL Tablets (tolterodine tablets)

Safety Update Review

Included in Medical Officer review dated March 5, 1998.

MEMORANDUM

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

DATE: March 6, 1998

FROM: Lisa A. Kammerman, Ph.D., Team Leader (HFD-715) LAK 3/6/98

THROUGH: S. Edward Nevius, Ph.D., Division Director (HFD-715) SEN 3/6/98

TO: NDA 20-771

SUBJECT: Team Leader Memorandum: NDA 20-771 (Tolterodine)

This memorandum provides additional statistical comments on NDA 20-771, and on Dr. Baldeo Taneja's statistical review of the submission.

Dr. Taneja's comments on sponsor's results (p. 18 of his review)
For ease of discussion, the following table summarizes the results (p-values) of the sponsor's analysis of the three placebo-controlled studies (008, 009, and 010) contained in the submission. Dr. Taneja's review gives a detailed discussion of the analyses.

Summary of p-values for comparisons with placebo

		Endpoint (change from baseline at 12 weeks)		
Study #	Treatment Arm	Micturitions	Incontinence Episodes	Volume Voided
008	Oxybutynin 5 mg	.0680	.023	.0001
	Tolterodine 2 mg	.0022	.22	.0001
009	Tolterodine 2 mg	.0045	.19	.0001
010	Oxybutynin 5 mg	.29	.0012	.0001
	Tolterodine 2 mg	.27	.13	.015

Note: Entries in table are taken from Dr. Taneja's review.

The applicant apparently performed repeated measures ANOVA to compare the time course among treatment groups for each of the endpoints within each of the studies (see page 2 of Dr.

Taneja's review). The p-values in the above table result from linear contrasts at Week 12. Given that the regulatory decision is being made on change from baseline at Week 12, Dr. Taneja should have addressed the appropriateness of this approach. However, his nonparametric analyses using change from baseline at Week 12 appear to support the findings presented by the applicant.

Volume voided

These results indicate that tolterodine and oxybutynin are superior to placebo in volume voided at 12 weeks relative to baseline. The medical reviewer considers volume voided to be the most important endpoint for evaluating physiological changes.

Micturitions

For the micturitions endpoint, my conclusion is that tolterodine 2 mg is significantly better than placebo. This was demonstrated in two of the studies (008 and 009). Because oxybutynin did not beat placebo in Study 010, the lack of assay sensitivity for this endpoint may explain the nonsignificant comparison between tolterodine 2 mg and placebo.

As Dr. Taneja's review indicates, the protocols for these studies were powered for this endpoint. I agree with his general concern that oxybutynin, a product approved for the proposed indication, did not beat placebo in two of the studies. This is especially true for Study 010. Dr. Taneja's review should have explored potential reasons for Study 010's inability to detect a significant difference from placebo for either treatment arms. For example, an assessment could consider whether the conduct of Study 010 differed from the other studies, and whether study drug discontinuations made an impact.

Incontinence episodes

For the endpoint of incontinence episodes, tolterodine 2 mg did not beat placebo in any of the three studies. In contrast the oxybutynin treatment arm in the two studies containing an active control arm was significantly better than placebo. Thus the lack of statistical significance in these two studies cannot be explained by the absence of assay sensitivity for incontinence episodes. Study 009 did not contain an active control arm; thus, the issue of assay sensitivity cannot be addressed for this study.

Even considering that oxybutynin was superior to placebo in the two studies with an active control, one might argue the studies may have been underpowered to detect a tolterodine treatment effect. The results from Studies 008 and 010 suggest tolterodine apparently has a smaller treatment effect than oxybutynin; thus a larger study would be needed to detect a statistically significant difference between tolterodine 2 mg and placebo. A determination of the clinical relevance of such a difference would need to be made.

According to the medical officer and the statistical reviewer, these studies were similar in design. Therefore, under certain circumstances it may be possible to pool the data from these studies to estimate the treatment effect of tolterodine compared with placebo on the endpoint of incontinence episodes. The next section addresses this issue.

Applicant's pooled analysis:
Other than stating that the pooled analysis needed to be stratified by study, Dr. Taneja's review does not adequately critique the applicant's pooled analysis (summarized starting on page 14 of his review) nor indicate why the applicant submitted it. According to his review, the pooled analysis appears to have reclassified the patients randomized to tolterodine 2 mg: those who remained on tolterodine 2 mg throughout the study were called "tolterodine 2 mg"; those whose dose was reduced to tolterodine 1 mg were called "tolterodine 1 mg". On its face, the reclassification of patients is inappropriate; the data should be analyzed according to the way patients were randomized.

Typically in assessing endpoints from adequate and well-controlled studies, the results from each study needs to stand on its own. Under certain circumstances, appropriate analyses of pooled data can be used to provide an estimate of the treatment effect. For this NDA, the medical reviewer and statistical reviewer have indicated that the study designs were similar in design. Thus, a confidence interval on the difference between tolterodine 2 mg and placebo, constructed by stratifying on study and classifying patients according to the treatment group to which they were randomized, may be appropriate for providing an overall estimate of the treatment effect for the various endpoints.

Other unresolved issues

Adjustments for multiple endpoints
The issue of whether the analyses should have adjusted for multiple endpoints was not addressed in Dr. Taneja's review.

Interpretation of subgroup analyses
A more appropriate assessment of whether the treatment effects were consistent among the various subgroups defined by age, race, and gender would have included calculation of the mean treatment effect (i.e., drug - placebo difference) for the various subgroups.

Discrepancies in data
Dr. Taneja performed nonparametric analyses on datasets provided by the applicant. There are inconsistencies between the number of patients with data in these datasets and with what was provided in the study reports. For example, Dr. Taneja's analysis of Study 009 indicates that for number of micturitions, 128 patients randomized to tolterodine 2 mg and for number of incontinence episodes, 116 patient randomized to tolterodine 2 mg were included in the analyses. This contrasts with the applicant's analysis: for micturitions, 129 patients randomized to tolterodine 2 mg and for incontinence episodes, 117 patients randomized to tolterodine 2 mg were included in the analyses. These discrepancies should be addressed by the applicant.

Summary
As noted above, the statistical review failed to address several key issues that should be included in an addendum review. However, I do concur with Dr. Taneja's basic conclusions:

Reduction in micturitions per 24 hours from baseline to 12 weeks:

Tolterodine 2 mg was significantly better than placebo in two studies (008 and 009) but not the third (010).

Increase in volume voided per micturition from baseline to 12 weeks:

Tolterodine 2 mg was significantly better than placebo in all three placebo-controlled studies (008, 009, 010)

Reduction in incontinence episodes per 24 hours from baseline to 12 weeks:

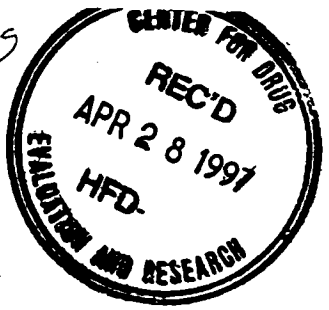
Tolterodine 2 mg was not significantly better than placebo in any of the three placebo-controlled studies.

cc:
Archival
HFD-580
HFD-580/DShames, ADunson
HFD-715/ENevius, LKammerman, BTaneja

LAK/WinWord7.0/Reviews/Tolterodine/Team Leader Memo 980305

HFD 530/ Boring

(823)



REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: **Dan Boring, Chair, HFD-530, Corporate Building Room N461**

FROM: Division of Reproductive and Urologic Drug Products HFD-580
Attention: Bob Seevers /S/ 4/24/97 Phone 301-827-4240

DATE: April 24, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Detrusitol tablets NDA 20-771

Company Name: Pharmacia & Upjohn

Established Name, including dosage form: Tolterodine tablets

Other trademarks by the same firm for companion products: None

Indications for Use: Treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms

Initial comments from the submitter: (concerns, observations, etc.) . None

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Response will be as timely as possible.

Consult #823 (HFD-580)

DETRUSITOL tolterodine tablets

The Committee noted one look-alike/sound-alike conflict: DETUSSIN. Since DETUSSIN is an OTC cough preparation, the Committee felt there was a low potential for confusion. There were no misleading aspects found with the proposed name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 8/18/97, Chair
CDER Labeling and Nomenclature Committee

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Microbiology Review

No microbiology review is required.

DEPARTMEN. ,F HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DF

NDA 20-771

JAN 16 1998

Pharmacia & Upjohn
Attention: Ilze K. Antons, M.S.
Senior Regulatory Manager
Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Antons:

Please refer to your pending March 24, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrusitol™ tablets (tolteridine tablets).

We also refer to your amendments dated August 29, 1997, November 18, 1997, November 18, 1997, and December 31, 1997.

We have completed our review of the chemistry section of your submission and have identified the following deficiencies:

The following items concern the drug substance:

Specifications

1. Although you have submitted an in-process limit test for in the drug substance, this test should be part of the drug substance release specifications. Please include a limit test for in the drug substance release specifications.

2. The analytical and stability data on the twelve batches of the drug substance submitted indicate that organic impurities are low (less than %). Most of these batches were used for toxicology and clinical studies which means that the proposed impurity specifications should be tightened: Total NMT %, CA 020045 NMT %, FC 97A NMT % and Sum of Unspecified Impurities NMT %. This change should also be made to the drug substance stability protocol.

The following items concern the drug product:

Regulatory Specifications

The organic impurities limits at expiry need to be tightened. Based on the stability data submitted, the limits should be: Total Organic Impurities NMT %, CA 020045 NMT %, and FC 97A NMT

%. The same change should be made in the post-approval stability protocol.

Container/Closure System

1. A deficiency letter has been sent to the in regard to their DMF for

2. You have not provided any information on the use of either a cap liner or innerseal for the bottles. If a cap liner or innerseal will be used, please submit appropriate descriptions of the nature and source of the materials.

Labeling

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely.

/S/ 1/16/98

Lisa D. Rarick, M.D.
Director,
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-771
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/RSeevers/MRhee
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: JMarkow/January 15, 1998/20771.01n
Initialed by:
final:

INFORMATION REQUEST (IR)

Dunson

MEMORANDUM OF TELECON

DATE: November 12, 1997

APPLICATION NUMBER: 20-771; Detrusitol

BETWEEN:

Name: Susan Mandabough
Phone: (616) 833-4070
Representing: Pharmacia & Upjohn

AND

Name: Robert Seevers, Ph.D., Moo-Jhong Rhee, Ph.D, and Mr. Alvis Dunson
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To discuss the addition of in-process controls for the super-potency tablets.

SUMMARY:

The sponsor was informed that in-process controls should be included in batch runs and especially at the end of the runs to ensure super-potency tablets are not being manufactured. The test need only be performed on the next two batches of each strength (1.0 mg and 2.0 mg) tablets with a concentration on testing at the end of the run where the problem occurred. Further testing would no longer be needed once satisfactory results on two additional runs for each strength have been achieved demonstrating that super-potency does not occur.

This proposal should be submitted as a minor amendment to the NDA with no affect on the review clock.

/S/ 12/8/97

Alvis Dunson
Project Manager

/S/ 12/5/97

Robert Seevers, Ph.D.
Chemist

cc: Original 20-771
HFD-580/Div. File
HFD-580/Alvis Dunson
HFD-580/RSeevers/MRhee

Drafted by: ADunson/November 20, 1997/n20771tc

Concurrence:
RSeevers11.22.97/MRhee12.2.97

TELECON

Dunson

NDA 20-771

APR 9 1997

Pharmacia & Upjohn
Attention: Ilze K. Antons, M.S.
Senior Regulatory Manager
Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Antons:

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

Name of Drug Product:	Detrusitol™ Tablets (tolterodine tablets)
Therapeutic Classification:	Standard
Date of Application:	March 24, 1997
Date of Receipt:	March 25, 1997
Our Reference Number:	20-771

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 24, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review, but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

/S/

4/7/97

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-771
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/DShames/HJolson/MRhee/AJordan/ADorantes/LKammerman/LPauls
DISTRICT OFFICE

Drafted by: ADunson/March 27, 1997/n20771ak

ACKNOWLEDGEMENT (AC)

MEMO OF TELECON

NDA: 20-771

Drug: DETROL (tolterodine tartrate tablets)

Date: March 18, 1998

Time: 2:00 PM

External Participant: Pharmacia & Upjohn

Tele: 616-833-8239

FDA Attendees:

Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Gregory Shawaryn - Regulatory Affairs

Conversation:

The following Clinical Pharmacology comments were conveyed:

1. Please submit the full study report for Study 97-OATA-036, including raw data and proper assay validation (inter- and intra-day precision and accuracy) for review. The full study report can be submitted for review post-approval.

2. The proposed *in vitro* dissolution test method is acceptable. However, it is recommended that the drug release specifications be changed to Q= \% at minutes. This issue should be addressed prior to approval.

/S/

Alvis Dunson 3/18/98

drafted: ADunson/3.18.98/n771tc6

cc:
IND Arch:
HFD-580
HFD-580/ADunson/DShames/LRarick/GBarnette

MAR 18 1998

MEMO OF TELECON

NDA: 20-771 **Drug:** DETROL (tolterodine tartrate tablets)

Date: March 12, 1998 **Time:** 11:00 AM

External Participant: Pharmacia & Upjohn **Tele:** 616-833-0856

FDA Attendees:

K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Susan M. Mondabaugh, Ph.D. - Director, U.S. Regulatory Affairs

Conversation:

The following comments were conveyed:

Since tolterodine is eliminated primarily through metabolism, a significant safety concern exists in patients with hepatic impairment. In pharmacology/toxicology studies in dogs it was observed that after nine days of treatment with tolterodine there was a percent increase in the Q-Tc interval . A single dose pharmacokinetic study was conducted in patients with hepatic cirrhosis and an increase in bioavailability and a decrease in clearance compared to that seen in normal healthy volunteers was observed.

Therefore, we request that you conduct a multiple-dose pharmacokinetic/pharmacodynamic study in hepatic impaired patients in which steady state pharmacokinetic and electrocardiogram (ECG) changes are assessed. Please submit a study design that includes the number of patients, duration of treatment, and time of ECG for review prior to initiating the study. This study may be conducted post-approval.

/S/ 3/16/98
Alvis Dunson

/S/ 3/18/98
Gary Barnette, Ph.D.

MEMO OF TELECON

NDA: 20-771

Drug: DETROL (tolterodine tartrate tablets)

Date: March 4, 1998

Time: 11:00 AM

External Participant: Pharmacia & Upjohn

Tele: 616-833-0856

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Daniel Shames, M.D. - Medical Officer, DRUDP (HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Alex Jordan, Ph.D. - Pharmacologist, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Kenneth King, Ph.D. - Vice President, Worldwide Regulatory Affairs
Susan M. Mondabaugh, Ph.D. - Regulatory Affairs

Conversation:

The sponsor wanted to clarify issues related to the physician labeling insert for DETROL. The following comments were conveyed:

1. The sponsor wanted to revise the introductory text in the **CLINICAL PHARMACOLOGY** section of the labeling to retain the reference to the anethesized cat data that indicated tolterodine shows a selectivity for the urinary bladder over salivary glands. The sponsor agreed to modify the statement and submit for review.

2. The sponsor indicated that the anethesized cat data was viewed as basic pre-clinical data to understand the drug and no advertising claim is expected.

/S/ 3/12/98
Alvis Dunson

/S/ 3/12/98
Lisa Rarick, M.D.

Post Meeting Note:

The sponsor faxed an unofficial version of the proposed carton and container labels for Division comment on February 24, 1998, followed by an official submission on February 25, 1998.

drafted: ADunson/3.5.98/n771tc4

Concurrences:
GBarnette/AJordan/DShames3.9.98/LRarick3.10.98

cc:
IND Arch:
HFD-580
HFD-580/ADunson/DShames/LRarick/GBarnette/AJordan

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Advisory Committee Meeting Minutes

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

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Federal Register Notices

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