

The most commonly reported adverse events by relation to treatment (Table 21 Vol. 26/51 pg. 101) were evaluated. As would be expected, dry mouth and constipation were the adverse events reported in patients treated with tolterodine ER that were most commonly considered treatment related. Three common adverse events (dry mouth, constipation, and headache) were analyzed in subgroups defined by gender, age, and metabolizer type (see Table #6). Increased incidence of selected adverse events were reported in women, in the elderly (>65 years), and in extensive metabolizers in the safety population taking tolterodine ER.

Table #6-Incidence of the Most Frequent Adverse Events in Study -007 by WHO Body System in Safety Population taking Tolterodine ER 4 mg qAM by Sex, Age, and Metabolizer Type Subgroups

(Created by MO from Table 25, 26, & 27 Vol. 1/51 p. 320-322)

WHO Body System Preferred Term	Male		Female		<65 yrs		>65 yrs		EM		PM	
	n	%	n	%	n	%	n	%	n	%	n	%
Mouth dry	13	14.4	105	25.3	66	22.7	52	24.3	98	24.9	6	20.7
Constipation	3	3.3	27	6.5	17	5.8	13	6.1	26	6.6	1	3.4
Headache	3	3.3	29	7.0	24	8.2	8	3.7	26	6.6	1	3.4

There were four patients who reported urinary retention during the study. Their patient narratives are summarized: **Patient 2814**: a 70-year-old female on tolterodine ER who complained of mild urinary retention on treatment day 5 and her post-void residual volume was 134.8 ml. She remained on study drug and the retention was considered as unrelated to study medication; **Patient 3189**: a 73-year-old male on tolterodine ER who was withdrawn from the study due to moderate urinary retention starting on treatment day #3; the investigator assessed the event as unrelated to study medication; it was unclear from the patient's CRF if he recovered after stopping study treatment; **Patient 1288**: a 65-year-old female on placebo who complained of mild urinary retention on treatment day 2; she recovered; the investigator assessed the event as related to study medication; and **Patient 1136**: a 71-year-old male on tolterodine IR who complained of severe urinary retention starting on treatment day 6; the patient recovered and was withdrawn from study medication; the investigator assessed the event as related to study medication.

4.10.3 Discontinuations due to AE

Adverse events caused premature withdrawal of 27 tolterodine ER subjects with 77 AEs and 33 placebo subjects with 78 AEs. A comparison of selected adverse events causing premature withdrawal is presented in Table #7. The AEs selected were those known to be affected by muscarinic receptor antagonists, were gastrointestinal AEs, or were cardiovascular AEs.

Table #7-Adverse Events Causing Premature Withdrawal
(Created by MO from Table 25 Vol. 2 pg. 77-82)

	Tolterodine ER Subject Number	Placebo Subject Number
Abdominal pain	1155, 1755	2572
Constipation	1080, 1155, 1199, 1755, 1930	1219, 1495, 1764, 2745
Ileus		2026
Intestinal obstruction		1752
Mouth dry	1059, 1125, 1155, 1412, 1737, 1755, 1807, 1930, 2498, 2536, 2842, 3158	1219, 1415, 1586, 2615, 2745, 3113
Nausea	1059, 1930	1167, 1415, 1696, 1851, 2293, 2410, 2799
Palpitation	1930	
Pericarditis		2117
Sudden death	2404	
Urinary retention	3189	
Vision abnormal	1078	1851
Vomiting	1930, 2536, 2851	1696, 2410
Additional AEs	49	54
Total AEs	77	78

4.10.4 Changes in lab values

No clinically relevant changes in laboratory assessments or ECG measurements were noted.

A total of 21 ml of blood was withdrawn at Visit 1 and 14 ml at Visit 4. Clinical chemistry and hematology analyses were performed in three central laboratories, one for each continent that contained study centers. The laboratories were [redacted]

[redacted]; was performed at a single laboratory, [redacted]. During the study, [redacted] changed its name to [redacted]. [redacted] PK samples were not collected as part of this trial.

[redacted] evaluated all ECGs. ECGs were obtained in a total of 174 patients (placebo=54, tolterodine ER=59, tolterodine IR=61) in selected centers in the United States. The protocol stated the patients in this substudy should be elderly (≥ 65 years). Of the 174 patients that had ECGs, 154 were ≥ 65 years. All ECGs obtained were included in the results regardless of subject age. Mean QTc increased 2.7 msec in the tolterodine ER group and decreased 3.5 msec in the placebo group. A decrease in mean QTc dispersion was observed in all treatment groups. No subject had a QTc on treatment that measured >500 msec at Week 12.

One tolterodine ER subject (#1588) had a borderline QTc at baseline (461 msec) and a prolonged QTc at Week 12 (475 msec). Subject #1588 was a 74-year-old female patient who had a medical history of diabetes mellitus and obesity.

Two tolterodine ER subjects (#1083 and #1412) had a prolonged QTc both at baseline and at Week 12. Subject #1083 was a 78-year-old male patient who had a baseline QTc of 506 msec and a Week 12 QTc of 492. He had a medical history of hypertension and an unspecified bundle branch block. Subject #1412 was a 78-year-old female who had a baseline QTc of 475 msec and a Week 12 QTc of 475. She had a medical history of hypertension.

No tolterodine ER subjects changed QTc >60 msec from baseline to Week 12.

Reviewer's comment:

- 1) **The reported QTc changes do not appear to be clinically significant.**
- 2) **The sponsor exceeded the goal of obtaining at least 90 ECGs in subjects ≥ 65 years.**

4.10.5 Changes in physical exam

No physical exam assessments were made in this study at screening, during treatment, or post treatment visits.

4.11 Reviewer's assessment of safety and efficacy

In Study 98-TOCR-007, treatment with tolterodine ER 4 mg qAM in patients with overactive bladder resulted in a highly statistically significant decrease in the number of incontinence episodes per week after 12 weeks treatment as compared with placebo. Tolterodine ER treatment was also associated with a statistically significant decrease in the number of micturitions per 24 hrs and in the number of pads used per 24 hrs after 12 weeks treatment when compared with placebo. **It is unclear whether these are clinically significant decreases.** Tolterodine ER treatment resulted in a statistically significant increase in the mean volume of urine voided/micturition at week 12 compared with placebo. **It is unclear whether this is a clinically significant increase.**

In Study 98-TOCR-007, more subjects reported a statistically significant improvement in the perception of urgency on tolterodine ER compared to placebo. A greater proportion of subjects on tolterodine ER 4mg qAM compared to placebo reported improvement in the perceptions of their bladder condition over the 12-week treatment period. A statistically significant higher proportion on tolterodine ER reported benefit of treatment at the end of the 12-week treatment.

In Study 98-TOCR-007, dry mouth and constipation were the most frequent adverse events related to treatment and reported in patients treated with tolterodine ER. No new major safety concerns were evident from the submitted serious adverse events, premature withdrawals, clinical laboratory assessments, and ECG data. Differences in the safety profile of tolterodine ER 4 mg qAM were identified based on age, gender, and metabolism. Increased incidence of selected adverse events were reported in women, in the elderly (>65 years), and in extensive metabolizers.

5.0 CLINICAL TRIAL 98-TOCR-007B: Long-term safety and efficacy of tolterodine prolonged release capsules. An open-label, uncontrolled, multinational study in subjects with symptoms of overactive bladder.

5.1 Objectives

The primary objective of this trial was to assess the safety of tolterodine extended release capsules 4 mg qAM over a 12-month treatment period in adult subjects with urge incontinence who had completed the original trial, 98-TOCR-007.

The secondary objective was to evaluate the efficacy of tolterodine extended capsules 4 mg qAM over a 15 month-treatment period in adult subjects with urge incontinence who had completed the original trial, 98-TOCR-007.

5.2 Design

This was a multicenter, multinational, open-label, nonrandomized, uncontrolled extension trial. Safety endpoints were assessed over the 12-month period. Efficacy endpoints were assessed at 3 and 12 months.

5.3 Study population

It was planned that the trial would enroll 1200 subjects at 160 investigator sites with 8 subjects per investigator.

The data from 410 subjects were included in the interim safety report submitted with this NDA on February 28, 2000. The data from 1072 subjects from 147 sites with a cut-off date of April 30, 2000 were included in the interim safety report submitted in Amendment #4-Safety Update on June 28, 2000.

5.3.1 Demographics

Demographic data in Amendment #4 was presented with the subjects divided into two groups: 12-month population (n=135) and 6-month population (n=1072). Similar to 98-TOCR-007, the study population was overwhelmingly female (82% & 86%), white (96%), and had a mean subject age of 60 years.

5.4 Inclusion and exclusion criteria

To be included in the study, patients had to have fulfilled all eligibility criteria before randomization in the original protocol, 98-TOCR-007 and completed the double blind 12-week treatment period. They had to be able and willing to correctly complete the micturition charts and have signed informed consent.

Patients were excluded if they demonstrated poor compliance in 98-TOCR-007, had concurrent use of another investigational medication, were being treated with potent CYP3A4 inhibitors or were expected to start such treatment during the trial, had an ongoing serious adverse event in 98-TOCR-007, were pregnant or nursing, or were female patients of childbearing potential not using reliable contraceptive methods.

Number of Pages
Redacted 19



Draft Labeling
(not releasable)

5.5 Procedures

Visit 6 of trial 98-TOCR-007 was Day 1 of 98-TOCR-007B. At this visit, a micturition chart was dispensed and any change in concomitant medication was recorded. Ongoing adverse events were reported and three months of trial medication was dispensed.

At one month \pm 1 week on treatment, the subject was contacted by telephone to document any spontaneously reported adverse events, any changes in ongoing adverse events, and any changes in concomitant medications.

During Visit 7 (at 3 months \pm 2 week on treatment), blood samples for clinical chemistry and hematology were obtained, the micturition chart was collected, QoL questionnaires were completed, perception of bladder condition and perception of urgency were assessed, medication compliance was assessed, changes in concomitant medications were recorded, and adverse events documented. Trial medication was dispensed for 3 months. If telephone contact(s) were scheduled instead of a visit(s) at Visit 8, or Visit 8 or 9, trial medication was dispensed for 6 or 9 months.

During Visit 8 (at 6 months \pm 2 week on treatment), changes in concomitant medications were recorded, and adverse events documented. This visit could occur by telephone contact or as a clinic visit. If a visit occurred, medication compliance was assessed and trial medication was dispensed.

During Visit 9 (at 9 months \pm 2 week on treatment), changes in concomitant medications were recorded, and adverse events documented. This visit could occur by telephone contact or as a clinic visit. If a visit occurred, medication compliance was assessed, a micturition chart was dispensed, and trial medication was dispensed.

During Visit 10 (at 12 months \pm 2 week on treatment), blood samples for clinical chemistry and hematology were obtained, the micturition chart was collected, QoL questionnaires were completed, perception of bladder condition and perception of urgency were assessed, medication compliance was assessed, changes in concomitant medications were recorded, and adverse events documented. If required according to country specific regulations, a urine pregnancy test was performed for female subjects of childbearing potential.

During the Post-treatment follow-up visit (at one week after end of treatment or withdrawal), changes in concomitant medications were recorded, and adverse events documented. This visit could occur by telephone contact or as a clinic visit.

5.6 Evaluation criteria

The primary endpoints were safety endpoints: the occurrence of adverse events grouped according to WHO preferred term, the occurrence of withdrawals over a 12-month treatment period, and change in laboratory variables over a 15-month treatment period. The secondary endpoints were efficacy endpoints: change in mean number of incontinence episodes per week, change in proportion of micturitions associated with urgency, change in mean number of micturitions per 24 hours, change in mean volume voided per micturition, change in subject's perception of bladder condition, change in subject's perception of urgency and change in QoL

scores over a 15-month treatment period. Visit 2 in the original trial 98-TOCR-007 was used as the baseline.

5.7 Withdrawals, compliance, discontinuations

Subjects were prematurely withdrawn from the trial if, in the opinion of the investigator, it was medically necessary, or if it was the subject's wish. If pregnancy was discovered, the trial medication was immediately discontinued and the subject withdrawn from the trial. If a subject did not return for a scheduled visit, every effort was to be made to contact the subject.

As of April 30, 2000, thirty (22.2%) subjects from the 12-month population and 210 (19.6%) subjects from the 6-month population were prematurely withdrawn from the study for any reason. Only 10.9% of the tolterodine ER arm in 98-TOCR-007 prematurely withdrew. An adverse event (AE) was the most common reason subjects were prematurely withdrawn in Study -007B (37% of all reasons for withdrawal in the 6-month population and 47% of all reasons for withdrawal in the 12-month population). Similar relative percentages of subjects based on length of trial were prematurely withdrawn (See Table #8).

Table #8: 98-TOCR-007B Subjects Prematurely Withdrawn from Study Compared to Tolterodine ER Arm from 98-TOCR-007
(Created by MO from Item 9: Safety Update Report, Table 7, and pg. 18)

	Total Number of Subjects	Number Withdrawn (% of total number)	Number Withdrawn due to AE (% of total number)
12-month population	135	30 (22.2%)	14 (10.4%)
6-month population	1072	210 (19.6%)	77 (7.2%)
Tolterodine ER arm from 98-TOCR-007 (12-week)	505	55 (10.9%)	27 (5.3%)

5.8 Efficacy analyses

Two efficacy analyses populations will be used when the study is completed:

- 1) Intention-to treat (ITT): All subjects who entered the 12-month follow-up period with missing values substituted with last value carried forward
- 2) Completers: All subjects who completed the 12-month follow-up period, Missing values will not be imputed.

No 98-TOCR-007B efficacy data has been submitted to date.

5.9 Safety analyses

Based on the data submitted as of the cut-off date of April 30, 2000, the extent of exposure to tolterodine ER in the 12-month population was >120 patient-years with 108 patients completing 12 months or more of exposure. Based on the data submitted as of the cut-off date of April 30, 2000, the extent of exposure to tolterodine ER in the 6-month population was >700 patient years with 941 patients completing 6 or more months of exposure.

5.9.1 Serious Adverse Events

As of the cut-off date of April 30, 2000, seven SAEs, including one sudden death (Patient 1161-Center 203 US), were reported in the 12-month population and 71 SAEs, including the same one sudden death (Patient 1161) and one death from inflicted injury (Patient 3099-Center 30 BE who was strangled by her husband), were reported in the 6-month population.

The sudden death (Patient 1161) was reported in a 70-year old female who was found dead at home after 263 days on tolterodine ER 4 mg qd. It is unknown if an autopsy was obtained. The CRF for her participation in Study -007B was reviewed. It stated that the sudden death was due to coronary artery disease. It did not list coronary artery disease as having been diagnosed prior to the patient's death. The Study -007B Narratives for Patients Reporting Serious Adverse Events (in Amendment #4 Item 9: Safety Update Report Appendix 5 pg. 82) stated that Patient 1161's sudden death was due to a possible heart attack. It also stated that the patient's medical history included hypertension, hypothyroidism, arthritis, hiatal hernia, and depression and the twelve concomitant medications included testosterone, alprozalam, losartan, celecoxib and omeprazole. The investigator considered the event unrelated to study treatment.

One patient (Patient 1687-Center 239 US) in the 6-month population reported atrial fibrillation, however it occurred 20 days after discharge following coronary bypass grafting due to an acute myocardial infarction.

Two patients (Patient 1844-Center 47 CA and Patient 3030-Center 160 FR) reported pregnancy while on study treatment. Their Study -007B CRFs and Narratives were reviewed. No information regarding the outcome of either pregnancy is currently available.

Patient 1844 was 41 years old and had a negative pregnancy test on September 7, 1999. She forgot to return her unused medication at Office Visit 8 on March 27, 2000. She received 273 days of tolterodine ER with her last dose on March 26, 2000. She was withdrawn on April 3, 2000 due to a positive pregnancy test on that date. The adverse event record stated that her pregnancy "started" on March 27, 2000 and had no additional comments.

Patient 3030 was 26 years old and had a negative pregnancy test on July 14, 1999. She received 2 ½ months of tolterodine ER with her last dose on October 10, 1999. She was withdrawn on October 26, 1999 due to a positive pregnancy test on that date. The adverse event record stated that her pregnancy "started" on October 1, 1999 and had no additional comments.

Reviewer's comments:

- 1) The Sponsor was asked to submit the CRF for Patient 1161's participation in Study -007 and any additional available records such as hospital summaries, autopsy report, or death certificate. These records were requested to determine any potential etiology (such as arrhythmia) for her sudden death. On November 28, 2000 the Sponsor submitted Patient 1161's death certificate and Serious Adverse Event Report Form and stated there are no hospital summaries for the patient. The death certificate stated that no autopsy was performed and that the immediate cause of death was coronary artery disease.**

- 2) **The SAE tabulation and narratives were reviewed (from Item 9: Safety Update Report, Table 8 on pg. 19 and Appendix 5 on pg. 82-96). No pattern of unexpected SAEs were identified in the Study -007B data reviewed.**

5.9.2 Frequent Adverse Events

As of the cut-off date of April 30, 2000, dry mouth (28.9%), constipation (10.4%), upper respiratory tract infection (9.6%), headache (7.4%), xerophthalmia (6.7%), urinary tract infection (5.9%), fatigue (5.2%), and coughing (5.2%) were the most commonly reported events (>5%) in the 12-month population.

As of the cut-off date of April 30, 2000, dry mouth (18.9%), constipation (5.6%), and urinary tract infection (5.1%) were the most commonly reported events (>5%) in the 6-month population.

Reviewer's comments:

- 1) **The number of patients reporting AEs by body system and preferred term was reviewed (in Item 9: Safety Update Report, Table 6 on pg. 16-17). No pattern of unexpected AEs were identified in the Study -007B data reviewed.**

5.9.3 Discontinuations due to AE

See Section 5.7 Table #7 of this review.

Reviewer's comments:

- 1) **The Patients Reporting AE Leading to Withdrawal tabulation (in Item 9: Safety Update Report, Appendix 4, pg. 79-81) was reviewed. The most common reported AEs leading to withdrawal in Study 007B were dry mouth (n=20 in 6-month population or 1.9% of 6-month population), headache (n=4 in 12-month population or 3% of 12-month population), and dizziness (n=3 in 12-month population or 2.2 % of 12-month population). Two patients in the 6-month population withdrew due to urinary retention. No patterns of unexpected SAEs leading to withdrawal were identified.**

5.9.4 Changes in lab values

No ECG measurements were planned in the protocol to take place during or post-treatment in Protocol 98-TOCR-007B.

Reviewer's comments:

- 1) **The change in laboratory values reported as AEs (in Item 9: Safety Update Report, Table 4 and Table 5 on pg. 14-15) was reviewed. One patient (#3049) in the 12-month population and one patient (#1512) in the 6-month population were reported to have increased hepatic enzymes. No clinically relevant changes in laboratory values were noted.**

5.9.5 Changes in physical exam

No physical exam assessments were planned in the protocol to take place before, during, or post-treatment (see Protocol 98-TOCR-007B: Schedule of Events Item 9: Safety Update Report pg. 40).

5.10 Reviewer's assessment of safety and efficacy

No assessment can be made regarding the efficacy of tolterodine extended release demonstrated in Study 98-TOCR-007B since no efficacy data was submitted in the interim reports.

In the 4-month Safety Update of Study 98-TOCR-007B, dry mouth and constipation were the adverse events most frequently reported in both the 6-month and 12-month populations. No new safety concerns were evident from review of the 6-month and 12-month population reported adverse events, serious adverse events, premature withdrawals, and clinical laboratory assessments when compared to the safety concerns previously reported with tolterodine IR.

6.0 SAFETY UPDATE REPORT

The 4-month Safety Update Report was submitted as Amendment #4 on June 28, 2000 and contained only an interim report on protocol 98-TOCR-007B. It is reviewed in Section 5 of this NDA. The data cut-off date for the 4-month Safety Update was April 30, 2000.

7.0 OVERVIEW OF EFFICACY

In Study 98-TOCR-007, treatment with tolterodine ER 4 mg qAM in patients with overactive bladder resulted in a highly statistically significant decrease in the number of incontinence episodes per week after 12 weeks treatment as compared with placebo. Tolterodine ER treatment was also associated with a statistically significant decrease in the number of micturitions per 24 hrs and in the number of pads used per 24 hrs after 12 weeks treatment when compared with placebo. **It is unclear whether these are clinically significant decreases.** Tolterodine ER treatment resulted in a statistically significant increase in the mean volume of urine voided/micturition at week 12 compared with placebo. **It is unclear whether this is a clinically significant increase.**

In Study 98-TOCR-007, more subjects reported a statistically significant improvement in the perception of urgency on tolterodine ER compared to placebo. A greater proportion of subjects on tolterodine ER 4mg qAM compared to placebo reported improvement in the perceptions of their bladder condition over the 12-week treatment period. A statistically significant higher proportion on tolterodine ER reported benefit of treatment at the end of the 12-week treatment.

PP analyses were similar to those of the ITT analysis. Subgroup analyses of the ITT populations by gender, age, race and metabolizer phenotype revealed few differences among groups in three micturitions chart variables and nothing that would lead to recommending treatment differences among groups. It should be noted that very few subjects were non-Caucasian.

Efficacy was demonstrated in the Phase 3 trial 98-TOCR-007 for tolterodine ER 4 mg, however no Phase 3 data was presented to confirm the efficacy of tolterodine ER 2 mg. Limited efficacy data is available for tolterodine ER 2 mg, since it was evaluated in only 29 patients in the Phase 2 dose-effect study 97-TOCR-002.

8.0 OVERVIEW OF SAFETY

Dry mouth, constipation, and headache were the most frequent adverse events reported with tolterodine ER. No new major safety concerns were evident from the review of tolterodine ER reported adverse events, serious adverse events, premature withdrawals, ECG and clinical laboratory assessments when compared to the safety concerns previously reported with tolterodine IR.

Differences in the safety profile of tolterodine ER 4 mg qAM were identified based on age, gender, and metabolism. Increased incidence of selected adverse events were reported in women, in the elderly (>65 years), and in extensive metabolizers.

9.0 COMMENTS ON PROPOSED LABELING

9.1 Regulatory Labeling History

Since the tolterodine ER label will be identical to the tolterodine IR label in many sections and similar to the tolterodine IR label in many other sections, the chronological regulatory labeling history of tolterodine IR and tolterodine ER will be presented. A teleconference was held with the sponsor to clarify issues related to the physician labeling insert for tolterodine IR on February 23, 1998. The comments conveyed to the sponsor included:

- All active comparator claims to oxybutynin should be removed from the labeling. The studies provided in the NDA were not designed to support such comparisons.
- There is evidence that tolterodine IR may not be as effective as oxybutynin at the reported dose, however, we expect to recommend approval of this product.
- "Pooling" of the data may not be acceptable and we recommend that the "pooled" data not be presented.
- No dose-ranging study for a comparison of effectiveness and safety between tolterodine IR and oxybutynin was performed.
- The sponsor asked if data provided in the NDA that included claims of improved dry mouth tolerability could be promotionally advertised. The sponsor was told that the studies were not designed to provide substantial supporting evidence that tolterodine IR is superior to current therapeutic options in terms of side effects. The dry-mouth comparison issue can be addressed as part of a phase 4 study.

Initial labeling was reviewed and comments with revisions sent to the sponsor on February 29, 1998.

A teleconference was held with the sponsor on March 4, 1998 to clarify the sponsor request to revise the introductory text in the CLINICAL PHARMACOLOGY section of the labeling to retain the reference to the anesthetized cat data that indicated tolterodine shows a selectivity for the urinary bladder over salivary glands. The sponsor indicated that the anesthetized cat data was viewed as basic pre-clinical data to understand the drug and no advertising claim is expected.

Draft labeling in the submissions from the sponsor dated February 25, 1998 (carton and container labels), March 6, 1998 (sample tray for blisters), and March 25, 1998 (physician package insert) was accepted by the agency. Supplemental New Correspondence (SNC)

regarding the label was submitted as Amendment 027 on June 12, 1998 and was the final version of the tolterodine IR label.

On August 23, 1998, the sponsor was notified that the Division would consider labeling changes the sponsor feels are supported by the completed PK study in children. They were also told that these changes, if accepted, would not affect the sponsor's claim for future pediatric exclusivity because additional safety and efficacy data would still be needed to adequately label Detrol™ for pediatric use. Additional concerns about the potential for Detrol™ to cause QT interval prolongations, in particular regarding the reported case of a 12-year old who experienced heart block after receiving 1 mg of Detrol™, were transmitted.

Supplement-Labeling Revision (SLR-002) to NDA 20-771 was submitted on January 12, 1999. It updated the information in the package insert with respect to drug interaction. On November 10, 1999, the sponsor was notified that the review of SLR-002 had been completed and agency had two recommendations for revisions to the Package Insert. The sponsor did not accept these recommendations and negotiations with DRUDP Clinical Pharmacology & Biopharmaceutics reviewers are continuing to present.

Supplement-Labeling Revision with Clinical Information (SE8-004) to NDA 20-771 was submitted on December 22, 1999. It presented clinical data from Protocol 98-TOCR-007, which was performed. No new information relative to NDA 20-771 was provided in this supplement to the Chemistry, Nonclinical Pharmacology and Toxicology, or Human Pharmacokinetics and Bioavailability sections. However, labeling revisions were proposed to the DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, and ADVERSE EVENTS sections. The Sponsor was sent an approvable action letter on October 23, 2000 when no response had been received from the sponsor regarding Agency revised Package Insert sent on October 4, 2000. A resubmission containing Sponsor revisions to the proposed label was received on October 27, 2000 and is under review.

Supplement-Labeling Revision (SLR-006) to NDA 20-771 was submitted as CBE (Changes Being Effected) on May 31, 2000 and was approved. It added a toll-free number and website address to the carton for complimentary samples of Detrol™ tablets.

Supplement-Labeling Revision (SLR-007) to NDA 20-771 was submitted on June 9, 2000. It is currently under review. It proposes changes to five sections of the Physician Insert: CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, OVERDOSAGE, AND DOSAGE AND ADMINISTRATION. The current approved INDICATIONS AND USAGE section is:

Detrol™ Tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

The proposed INDICATIONS AND USAGE section is:

Detrol™ Tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, and/or urge incontinence.

Supplement-Labeling Revision (SLR-008) to NDA 20-771 was submitted as CBE (Changes Being Effected) on October 5, 2000 and is currently under review. It detailed nine changes that

had been made to four different sections of the Package Insert: CLINICAL PHARMACOLOGY, PRECAUTIONS (General, Information for Patients, and Pregnancy subsections), OVERDOSAGE, and ADVERSE REACTIONS. It added a new subsection, Postmarketing Surveillance, to the ADVERSE REACTIONS section. The attached letter also described that these nine changes were implemented in production in mid-August 2000. The letter also stated that due to an internal miscommunication there had been a delay in notifying the Agency that the changes had taken place.

It would be optimal to address all outstanding tolterodine IR labeling revisions at the same time the tolterodine ER label is negotiated. This would require completion of negotiations with the Sponsor regarding NDA 20-771 SLR 002, SLR 006, SLR 007, and review of SLR 008.

Specifically regarding the tolterodine ER label, the Sponsor requested feedback from the Agency in their June 8, 2000 letter regarding _____ as their primary and DETROL™ LA as their secondary trademark choice for tolterodine ER. The Office of Post-Marketing Drug Risk Assessment (OPDRA) Consultation dated October 2, 2000 recommended not using the modifier _____ " for tolterodine extended-release capsules due to safety concerns. OPDRA did not find the alternate modifier "LA" objectionable. The Sponsor then requested feedback from the Agency regarding their new primary trademark choice, _____. On December 7, 2000, the Sponsor submitted Amendment #12 which included two sets of mock-up labeling with one set using the suffix LA and one set using the suffix _____. The Division notified the Sponsor that _____ was unacceptable due to safety concerns and that DETROL™ LA was acceptable during a teleconference on December 13, 2000.

The Sponsor was notified in an Information Request Letter dated November 17, 2000 that the phrase "_____ capsules" is unacceptable and should be replaced with "extended-release capsules". The general term per USP terminology is Modified Release, divided into delayed release and extended release. With this terminology, _____ release is not used.

9.2 Proposed Labeling

All outstanding tolterodine IR labeling revisions that were pertinent to tolterodine ER, except those involving SLR 008, were included in the Agency proposed tolterodine ER package insert, which was faxed to Sponsor on November 27, 2000 (see Attachment C).

A Consultation from the Division of Cardio Renal Drug Products regarding evaluation of ECG labeling and QT/QTc data presented in Items 8/10 of NDA was completed on December 5, 2000. Based on the limited ECG data requested to be reviewed, the reviewer concluded that the effect of tolterodine on the QT interval in humans cannot at this time be determined. The reviewer also stated that tolterodine is the R-enantiomer of terodiline, which is incorrect. The reviewer did not have extensive information regarding QT prolongation with tolterodine IR, which includes general correspondence submitted by the Sponsor to NDA 20-771 on August 18, 1999 (which included a document summarizing the Sponsor's assessment of any proarrhythmic properties of tolterodine; OPDRA consults, and a memo from Marianne Mann, M.D. Deputy Director dated January 24, 2000. In addition, the Sponsor submitted to _____ on December 12, 2000 an information amendment relative to tolterodine and its possible association

with prolongation of QT interval. Based on this additional information, I do not agree with the conclusions of the Cardio Renal consultation.

Reviewer's comments:

- 1) **The label proposed by the Sponsor displays the Incidence of Adverse Events Reported in $\geq 5\%$ of Patients Treated and displays only three AEs by WHO preferred terms. It is the opinion of the reviewer that the short list of AEs in the proposed table may create a false sense of safety regarding tolterodine ER]. The frequency cut-off in the AE table has been changed to $\geq 1\%$.**

- 2) **The Draft Guidance for Industry "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics" was distributed for comment purposes in May 2000. It makes several recommendations pertinent to the proposed tolterodine ER Adverse Reaction table:**
 - **"Data in the primary table should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative." This recommendation would support including all patients from placebo-controlled or dose-response studies. It would exclude utilizing active-controlled data, single arm trial data (such as from open label extension patients), or the overall database in the table.**
 - **"Ordinarily, a frequency cut-off appropriate to the size of the database and design of the trial should be identified and only adverse reactions occurring at that frequency and above should be presented in the table." This recommendation would support either continuing to use the $\geq 1\%$ frequency cut-off or changing to a new frequency cut-off. The Draft Guidance does not recommend a specific frequency cut-off, such as Adverse Events Reported in $\geq 1\%$, $\geq 2\%$, or $\geq 5\%$ of Patients Treated.**
 - **"Data presented should be organized by body system and, within body system category, by order of decreasing frequency." This recommendation would support listing both the body system and specific adverse reaction.**
 - **"To help place in perspective the significance of adverse reactions data obtained from clinical trials, the data presentation should be preceded by the following statement, or an appropriate modification:**

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates."

This recommendation will be incorporated into the tolterodine ER label.
 - **"If relevant and not provided elsewhere, the commentary should include results of vital sign measurements such as blood pressure, heart rate, and electrocardiogram." This recommendation is pertinent to the body of information evaluating possible cardiac arrhythmias and tolterodine ER. EKG findings will be incorporated into the tolterodine ER label.**

- **“In characterizing overall adverse reactions experience, subjective and nonspecific terms (e.g., *well tolerated*) should be avoided, as they have no precise meaning and can be misleading.” This recommendation pertains to the new sentence in the proposed tolterodine ER label which begins:**

[TM] 4 mg once daily was generally well tolerated...

It is the reviewer's recommendation to delete this entire sentence.

- 3) The label proposed by the Sponsor does not contain any statements regarding the safety of tolterodine ER in subgroups. Health care practitioners need to be informed of any differences in the safety profile of tolterodine based on age, gender, race, or metabolism. Additional information on the subgroups of gender and age will be added to the label.**
- 4) A substantial amount of information would not be presented in the tolterodine ER label if the Incidence of Adverse Events Reported in $\geq 5\%$ of Patients Treated is displayed instead of the reviewer recommended $\geq 1\%$. Only three AE categories are listed in the Sponsor proposed $\geq 5\%$ tolterodine ER AE table as compared to the 13 AE categories which are listed in the reviewer proposed $\geq 1\%$ tolterodine ER AE table. The recommended frequency cut-off of $\geq 1\%$ would be the same as in the current approved tolterodine IR AE table.**
- 5) It is the reviewer's opinion that labels for urinary incontinence drugs are not ready to be standardized into class labeling. However, the goal is to be fair regarding labels for drug products with similar indications.**

10.0 PEDIATRIC STUDIES

To present, there have been no tolterodine ER pediatric studies conducted under ~~_____~~

One tolterodine IR pediatric study was conducted under ~~_____~~: Protocol 97-OATA-044 “Safety and pharmacokinetics of tolterodine 0.5, 1, 2 and 3 mg bid in patients between 5 and 10 years of age. An open controlled trial.” The 97-OATA-044 trial was initiated on April 21, 1998, completed on April 30, 1999, and the final study report was submitted on April 5, 2000 as Serial No. 131. The 3 mg bid dose was not given after one 2 mg bid subject withdrew due to tachycardia and one 2 mg bid subject withdrew due to disturbed accommodation. The Sponsor concluded from this trial that based on the combined safety, pharmacokinetic and efficacy data that tolterodine 1 mg bid may be the preferred dose for treatment of children aged 5-10 years. From my review of 97-OATA-044, I concluded that the Sponsor appeared correct in eliminating the 2 mg bid dose for pediatric subjects aged 5-10, however there were too few subjects (n=4) in the efficacy 1 mg bid incontinence episode group to conclude that 1 mg bid was the dose for this age group. I also raised concerns regarding the high AUC results for Poor Metabolizer (PM) patients.

During a May 15, 2000 teleconference, future pediatric tolterodine studies and questions regarding pediatric exclusivity were discussed. The Sponsor submitted their Proposed Pediatric Study Request to NDA 21-228 on June 28, 2000 as Amendment #5. They proposed two studies: Protocol 583E-URO-0084-020 “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 randomised, double blind, multinational study." And Protocol 583-URO-0084-018 "Pharmacokinetics, effect, and safety of tolterodine 2 and 4 mg once daily in children 11 to 15 years of age. An open, parallel group, study in patients with overactive bladder." Amendment #5 also included a statement that these studies comprised the pediatric study plan for tolterodine ER and a request for a partial waiver for patients younger than 5 years old.

During a November 29, 2000 teleconference, the Division discussed the tolterodine Written Request for pediatric exclusivity and notified the Sponsor regarding the tolterodine ER Pediatric Study Requirements under the Pediatric Rule:

11.0 RECOMMENDATIONS FOR REGULATORY ACTION

Pending satisfactory labeling negotiations with the sponsor, the reviewer recommends approval of NDA 21-228. In addition to the Reviewer's comments in Section 8.2 and Attachment C-Label Changes, it would be optimal that negotiations include the pertinent tolterodine IR labeling changes requested by the sponsor in NDA 20-771 SLR-002, SLR-006, and SLR-007.

BSI
Brenda S. Gierhart, M.D.
Medical Officer, DRUDP

12/19/00
Date

BSI
Dan Shames, M.D.
Deputy Director, DRUDP

12/19/00
Date

cc:Archival NDA 21-228
HFD-580 S. Allen/D. Shames/B. Gierhart

Attachment A-Definition of Terms

Term	Definition
b.i.d. or bid or BID	Twice a day
tolterodine modified release formulation	Tolterodine extended release (ER), tolterodine prolonged release (PR), and tolterodine once daily is understood to indicate the same formulation
qAM	Once daily taken in the morning
q.d. or qd or OD	Once daily

Attachment B-List of Abbreviations (Created by MO partially from Definitions Vol. 2 pg. 17)

Abbreviation/ Acronym	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CAD	Coronary artery disease
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CRF	Case Report Forms
CYP2D6	Cytochrome P-450 2D6
CYP3A4	Cytochrome P-450 3A4
DD 01	5-hydroxymethyl metabolite of tolterodine
DMEDP	Division of Metabolic and Endocrine Drug Products
DRUDP	Division of Reproductive Urology Drug Products
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ER	Extended release
EM	Extensive metabolizer
FDA	Food and Drug Administration
HRQOL	Health-Related Quality of Life
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IM	Immediate release
IRB	Institutional Review Board
ITT	Intent-to-treat (population)
KHQ	King's Health Questionnaire
LPH	Left posterior hemiblock
LS	Least square
MC	Micturition chart
mcg	Micrograms
MCS	Mental Component Summary
mg	Milligrams
MO	Medical Officer
N	Number (of subjects)
NDA	New Drug Application
OAB	Overactive bladder
PCS	Physical Component Summary

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

Safety Update Review

See Medical Officer's Review, page 42.

**APPEARS THIS WAY
ON ORIGINAL**

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

Pediatric Information

During a November 29, 2000 teleconference, the Division discussed the tolterodine Written Request for pediatric exclusivity and notified the Sponsor regarding the tolterodine extended release Pediatric Study Requirements under the Pediatric Rule:

~~_____~~

The pediatric age range of neonate (birth to one month) was waived after a review of the literature did not document the use of tolterodine under 3 months of age.

See Medical Officer's Review, page 48.

**APPEARS THIS WAY
ON ORIGINAL**



Farinas

Food and Drug Administration
Rockville MD 20857

NOV 16 2000

Sheldon Freedman, M.D.
3006 S. Maryland Parkway
Las Vegas, Nevada 89109

Dear Dr. Freedman:

Between June 12 and June 22, 2000, Mr. Anthony Keller, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #TOCR-007) of the investigational drug, Detrol[®] (tolterodine tartrate) tablets, performed for Pharmacia & Upjohn Company. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Keller presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to maintain adequate and accurate records.
 - a. Original subject diaries (micturation charts) were not available for inspection.

The diary for subject #1433 for August 28, 1999, had portions whited-out.
 - b. Subject #1555 did not have an informed consent form on file.
 - c. Subject #1201 did not complete page one of the health survey.
 - d. Numerous discrepancies were observed between the subjects' diaries and the information contained in the database. For example: the micturition diary for subject #1201 did not agree with the database on two occasions regarding the time of micturition, and on another occasion, the volume of urine passed was different between the diary and the database.
2. You failed to conduct your study in accordance with the approved protocol.
 - a. The protocol required that the subject numbers be assigned in "strict consecutive order"; however, subject #1959 was enrolled on June 2, 1999 while subject #1958

was enrolled on June 3, 1999. Also, study numbers 1931 through 1939 were assigned to subjects followed by assignment of number 1867.

b. Subject visits were not conducted within the timeframes specified by the protocol.

- 1) Subject #1433 was screened on May 21, 1999, and enrolled into the study on June 10, 1999. The time period between screening and enrollment is greater than the 14 days specified by protocol.
- 2) Subject # 1435 was screened on May 21, 1999, and enrolled into the study on June 16, 1999, exceeding the maximum of 14 days between visits as specified by the protocol.
- 3) Subject # 1511 was enrolled on July 15, 1999 (Visit 2), and returned for Visit 4 on September 27, 1999, a difference of 73 days. The protocol specified that the elapsed time between Visits 2 and 4 should be between 80 and 88 days.
- 4) Subject #1939 had Visit 2 on July 23, 1999, and Visit 4 on October 7, 1999, a difference of 76 days.

Because of the number and nature of the violations of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to ensure that these violations are not repeated in ongoing and future studies that you might conduct.

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

Sincerely yours,

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

**APPEARS THIS WAY
ON ORIGINAL**

cc:

HFA-224

HFD-580/Doc. Rm. NDA 20-771/S-004 and 21-228

HFD-580/Farinas

HFD-580/Shames

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP File #010202

HFD- 46/Blay

HFD-46/Huff

HFD-46/Martin

HFR-SW250/Singleton

HFR-SW250/Sherer

HFR-SW2520/Keller

CFN #

Field Classification: VAI

Headquarters Classification:

1)NAI

2)VAI

no response required

3)VAI-R

response requested

4)VAI-RR

adequate response received prior to issuance of VAI-R letter

5)OAI-WL

warning letter

6)OAI-NIDPOE

A response is therefore requested from the investigator that will outline how these deficiencies will be corrected or avoided in future studies.

Deficiencies noted:

inadequate consent form

inadequate drug accountability

deviation from protocol

inadequate records

failure to report ADRs

failure to obtain IRB approval

failure to personally conduct or supervise study

other

drafted/rab/10.26.00

reviewed:/Jmartin:11/2/00

final:jau:11/6/00

Note to Review Division and DSI Recommendation:

Our review of the information provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. 40 subjects were enrolled in the study. The inspector conducted a comprehensive review of the study-related records of 8 of the 40 enrolled subjects. The inspector reviewed all records for the presence of signed informed consent forms and performed spot checks of specific information for other study records. Our final classification of this inspection is Voluntary Action Indicated – Response Requested (VAI-R).

**APPEARS THIS WAY
ON ORIGINAL**



Jarinas

Food and Drug Administration
Rockville MD 20857

SFP 1 3 2000

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

Dear Dr. Mitcheson:

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

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

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

Sincerely yours,

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

cc:

HFA-224

HFD-580/Doc. Rm. NDA 20-771/S-004

HFD-580/Farinas

HFD-580/Hirsch

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP File #010136

HFD- 46/Blay

HFD-46/Huff

HFD-46/Martin

HFR-NE252/Kraychuk

HFR-NE250/Levitt

HFR-NE250/Hagan

CFN #

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI

no response required

3)VAI-R

response requested

4)VAI-RR

adequate response received prior to issuance of VAI-R letter

5)OAI-WL

warning letter

6)OAI-NIDPOE

Note to the File:

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

drafted/rab/8.30.00

reviewed:/

final:mgk 9/6/00

Note to Review Division and DSI Recommendation:

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

**APPEARS THIS WAY
ON ORIGINAL**



Joelinas

Food and Drug Administration
Rockville MD 20857

AUG 8 2000

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

Dear Dr. Antoci:

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

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

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

Sincerely yours,

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

cc:

HFA-224

HFD-580/Doc. Rm. NDA 20-771/S-004

HFD-580/Farinas

HFD-580/Hirsch

HFD-45/Reading File

HFD-46/Chron File

HFD-46/GCP File #010152

HFD- 46/Blay

HFD-46/Huff

HFD-46/Martin

HFR-NE252/Kraychuk

HFR-NE250/Levitt

HFR-NE2530/Murphy.

CFN#

Field Classification: NAI

Headquarters Classification:

 X 1)NAI

 2)VAI

 3)VAI-R

 4)VAI-RR

 5)OAI-WL

 6)OAI-NIDPOE

no response required

response requested

adequate response received prior to issuance of VAI-R letter

warning letter

drafted/rab/8.4.00

reviewed:/

Final:mgk 8/7/00

**APPEARS THIS WAY
ON ORIGINAL**

Note to Review Division and DSI Recommendation:

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

**APPEARS THIS WAY
ON ORIGINAL**

Gierhart

AUG 31 2000

MEMORANDUM

To:

NDA 20-771 Tolterodine Immediate Release
NDA 21-228 Tolterodine Release

Through:

Dan Shames, MD
Acting Deputy Director, HFD-580

From:

Brenda S. Gierhart, MD
Medical Officer, HFD-580

JSI
8/23/00

L. MD

Date:

August 31, 2000

Re:

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

Current submission:

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

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

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

Reviewer's comments:

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

Recommendation:

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

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

Original NDA 20-771

Original NDA 21-228

HFD-580 Division File

S. Allen, D. Shames, B. Gierhart, E. Farinas, HFD-580

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Inspection Site Selection Agreement

MEMORANDUM

Date: April 27, 2000

To: Roy Blay, Ph.D., Senior Regulatory Review Officer
OMP/DSI/GCPB1, HFD-46

From: Terri Rumble, Supervisory Project Manager, DRUDP,
HFD-580
Brenda Gierhart, M.D., Medical Officer
Evelyn Farinas, Project Manager

Subject: Request for Clinical Inspections
NDA 21-228
Pharmacia & Upjohn
Detrol (tolterodine tartrate) tablets

Protocol/Site Identification

After discussion with Dr. Gierhart, the following protocols/sites essential for approval have been identified for inspection by DSI. The indication for this drug

of the drug in a release format. This NDA provides for a reformulation

<u>Protocol #</u>	<u>Site (Name and Address)</u>
98-TOCR-007	Joseph Antoci, M.D. Medical Practice 160 Robbins Street
98-TOCR-007	Sheldon Freedman, M.D. Sheldon J. Freedman, M.D., Ltd. 3006 South Maryland Parkway, #430 Las Vegas, NV 98109
98-TOCR-007	David Mitcheson, M.D. Bay State Urologists, Inc. 1 Nevin Street, Suite 501 Brighton, MA 02135

Goal Date for Completion

Clinical Inspection Site Selection Agreement

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) 11/28/00. We intend to issue an action letter on this application by (action goal date) 12/28/00

Should you require any additional information, please contact Roy Blay, Ph.D., GCPB1, (7-7378).

Concurrence:

- Medical Team Leader
- Medical Reviewer
- Regulatory Project Manager

Distribution: NDA 21-228
 HFD-580/Division File
 HFD-580/Farinas
 HFD-46/Blay
 HFD-46/Waterman

Handwritten notes:
 ISI
 ISI
 ISI
 Deputy Dir
 4/27/00
 4/27/00
 4/28/00

APPEARS THIS WAY ON ORIGINAL