

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

MEDICAL REVIEW(S)

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HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

NDA: 21-228

Tolterodine Tartrate Extended Release

Medical Officer's Review
(Original NDA)

Date submitted: 2/25/00

CDER stamp date: 2/28/00

Date assigned: 3/8/00

CDER due date: 12/28/00

Review completed: 12/19/00

Key words: Tolterodine, urge incontinence, urinary frequency, urgency, overactive bladder, and extended release

Sponsor: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

Drug names:

Generic: Tolterodine tartrate extended release capsules

Trade: Unknown

Chemical: (R)-N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

Drug class: Muscarinic receptor antagonist

Administration route: Oral

Dosage form: Extended release capsule qAM

Strength: 2 mg and 4 mg

Proposed indication:

Related NDAs:

NDA 17-577

Oxybutynin chloride (DITROPAN) tablets; Alza
(Note: NDA transferred from Hoescht Marion Roussel in January 1998)

NDA 18-211

Oxybutynin chloride (DITROPAN) syrup; Alza
(Note: NDA transferred from Hoescht Marion Roussel in January 1998)

NDA 20-771

Tolterodine tartrate (DETROL) tablets; Pharmacia & Upjohn

NDA 20-897

Oxybutynin chloride (DITROPAN XL) extended release tablets; Alza

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1.0 RESUME

Tolterodine immediate release tablets (Detrol™ Tablets) were approved by the agency on March 25, 1998 for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. The sponsor now submits their first tolterodine modified release dosage form in NDA 21-228 for tolterodine prolonged release capsules. It should be noted that the modifier "prolonged release" is not an official dosage form in the United

States Pharmacopoeia (USP) monographs. The term "extended release" is used for Pharmacopoeia purposes and will be used in this review instead of "prolonged release". Tolterodine extended release capsules were evaluated in seven clinical trials enrolling 1659 patients. The Clinical/Statistical Data section of NDA 21-228 contains the final study reports of five phase 1 clinical pharmacology trials: 97-TOCR-001, 97-TOCR-003, 98-TOCR-005, 98-TOCR-006, and 98-TOCR-010; one phase 2 clinical pharmacology and dose-finding trial 97-TOCR-002; and one phase 3 clinical trial, 98-TOCR-007 with a long-term extension, 98-TOCR-007B.

Study 98-TOCR-007 was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design, phase 3 study in adult patients with an overactive bladder with symptoms of urge incontinence and urinary frequency. It compared tolterodine extended release (ER) capsules 4 mg qAM, tolterodine immediate release (IR) tablets 2 mg bid, and placebo during a 12-week treatment period. Study 98-TOCR-007 was undertaken for two reasons. Firstly, the sponsor wants to market an extended release formulation of Detrol™. Secondly, the sponsor wanted to demonstrate a statistically significant decrease in the number of incontinence episodes with tolterodine IR treatment compared with placebo. The three previous Detrol™ phase 3 trials (Studies 94-OATA-008, -009 and -010) submitted to NDA 20-771 did **not** demonstrate a statistically significant decrease in the number of incontinence episodes with tolterodine IR treatment compared with placebo. It should be noted that Studies 94-OATA-008, -009 and -010 were **not designed nor powered** to detect statistically significant differences in the number of incontinence episodes. This was because the change in the mean number of incontinence episodes per 24 hours from baseline to end of study (week 12) was a secondary efficacy measurement. The primary efficacy measurement for Studies 94-OATA-008, -009 and -010 was the change in the mean number of micturation per 24 hours from baseline to the end of the study (week 12). It should also be noted that 94-OATA-008 and -009 were comparative trials each with an oxybutynin arm and in both studies, the oxybutynin ITT populations were statistically superior to placebo in decreasing the number of incontinence episodes.

The primary efficacy variable for Study 98-TOCR-007 was the number of **incontinence episodes per week**, as calculated from data recorded on micturition charts. A decrease in the mean number of incontinence episodes per week at end of study (week 12) from baseline was demonstrated by tolterodine ER (-11.8 episodes or 53%) and placebo (-6.9 episodes or 30%). The treatment difference between tolterodine ER and placebo was 4.8 incontinence episodes per week, which was highly **statistically significant** ($p=.0001$). However, it is the reviewer's opinion that it is more relevant whether Study -007 demonstrated a **clinically significant difference** between the tolterodine ER treatment and placebo in the number of incontinence episodes per week, since statistical significance can be achieved simply by enrolling a large number of patients in a trial. For example, in Study 98-TOCR-007 a similar highly statistically significant ($p=.0005$) decrease in the mean number of incontinence episodes per week at end of study (week 12) from baseline was demonstrated by tolterodine IR (-10.6 episodes or 46%) when compared with placebo (-6.9 episodes or 30%). However, when the Study -007 tolterodine IR versus placebo treatment difference result was converted to the number of incontinence episodes per 24 hours, all four of the tolterodine IR placebo-controlled 12-week studies demonstrated a similar treatment difference (-0.4 or -0.5 episodes per 24 hours), although it was statistically

significant only in Study -007 (see Table #1). Study -007 was statistically significant for tolterodine IR because it enrolled 4 or 5 times more patients than the other trials.

Since statistical significance can be obtained simply by increasing the patient numbers, it is most important if a study demonstrates a clinically significant difference. It was not clearly prespecified in the Study -007 protocol what would constitute a clinically significant difference in the number of incontinence episodes per week. It is unclear whether tolterodine ER's 23% decrease in the mean number of incontinence episodes when compared to placebo (-4.8 episodes per week) is a clinically significant difference.

Table #1-Number of Incontinence Episodes per 24 Hours: Difference between DETROL (tolterodine IR) and Placebo for the Mean Change at Week 12 from Baseline

Study		DETROL 2 mg bid	Placebo	Difference
-007	number of patients	514	508	
	mean change from baseline	-1.5	-1.0	-0.5*
-008	number of patients	93	40	
	mean change from baseline	-1.3	-0.9	-0.5
-009	number of patients	116	55	
	mean change from baseline	-1.7	-1.3	-0.4
-010	number of patients	90	50	
	mean change from baseline	-1.6	-1.1	-0.5

*The difference between DETROL and placebo was statistically significant.

Regarding safety, no serious and unexpected safety concerns were revealed after 12 weeks of tolterodine ER treatment in Study -007. However, a subgroup analysis was performed specifically looking for any differences in the safety profile of tolterodine ER based on age, gender, race, or metabolism. There did appear to be a difference in safety profile of tolterodine ER based on age and gender.

The primary objective of the long-term study 98-TOCR-007B was to assess the safety of tolterodine ER capsules 4 mg over a 12-month treatment period in all patients who continued from the double blind Study -007. The secondary objective was to study the efficacy of tolterodine ER 4 mg over a 15-month period in those patients who had received tolterodine ER in the original double-blind study.

The Sponsor proposed tolterodine ER label in NDA 21-228 is similar to the Sponsor proposed tolterodine IR (Detrol™) label in NDA 21-771 SE8-004. Many of the same labeling changes proposed by the Agency after the review of NDA 21-771 SE8-004 are also proposed in this review. The Agency and the Sponsor share the labeling goal of creating as much consistency as possible with the tolterodine ER and tolterodine IR labels. An additional Agency labeling goal is to be fair regarding labels for drug products with similar indications. To obtain these goals, multiple changes to the Sponsor proposed label have been proposed (see Attachment C).

2.0 BACKGROUND

The overactive bladder, with symptoms of frequency, urgency and urge incontinence, affects millions of people throughout the world.¹ The current approved indication of tolterodine IR (Detrol™) Tablets is "for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence". The indication sought for tolterodine ER capsules in this NDA and for tolterodine IR (Detrol™) Tablets in NDA 21-771 S-007 is:

However, patients were included in the tolterodine ER Phase 3 trials only if they had both urinary frequency and urge incontinence. The term "overactive bladder" describes a symptom complex and is an attempt to "lump" together patients with any or all components of the symptom complex. It was defined in 1999 as:

Bladder overactivity should be able to be defined either by urodynamic studies or by symptoms. A reasonable definition would be that symptomatic bladder overactivity is a condition referring to the symptoms of frequency, urgency, and urge or reflex incontinence, either singly or in combination, when appearing in the absence of local pathological factors (e.g., urinary tract infection, stones, interstitial cystitis) explaining these symptoms.¹

The term "overactive bladder" is of such fairly recent vintage that it is not listed in the index of Campbell's Urology² or Harrison's Principles of Internal Medicine³. It is not listed in the International Continence Society (ICS) classification of voiding dysfunctions⁴, in the Urodynamic Society's Definition and Classification of Urinary Incontinence⁵, or in the "Expanded Functional Classification" of voiding dysfunction in Campbell's Urology⁶.

In the past, Urology "split" patients into smaller categories based on diagnosis, test results, or etiology. The International Continence Society (ICS) attempted to standardize the terminology of lower urinary tract function by heavily relying upon the patient's urodynamic testing results⁷. Other classification systems have relied upon the patient's specific Urologic diagnosis or whether the symptoms had a specific etiology, such as neurogenic. It is important to realize that this "lump" of patients labeled as having an overactive bladder may have many different diagnoses, etiologies, and test results, may be of any age or sex, and may exhibit a wide range in number and severity of symptoms.

In the submitted clinical study 98-TOCR-007, the sponsor included patients with an overactive bladder only if they demonstrate urinary frequency (on average >8 micturition per 24 hours) and

¹ Wein AJ and Rovner ES: The Overactive Bladder: An Overview for Primary Care Health Providers. *Int J Fertil Womens Med* 1999 Mar-Apr; 44 (2): 56-66.

² Walsh P et al, editors: *Campbell's Urology* 7th edition W.B. Saunders Company, Philadelphia, 1998.

³ Isselbacher K et al, editors: *Harrison's Principles of Internal Medicine* 13th edition McGraw-Hill, Inc., New York, 1994.

⁴ Abrams P, Blaivas JG, Stanton SL, Andersen JT: The standardization of terminology of lower urinary tract function recommended by the International Continence Society. *Int. Urogynecol J* 1990; 1:45.

⁵ Blaivas JG, Appell RA, Fantl JA, Leach G, McGuire EJ, Resnick NM, Raz S, Wein AJ: Definition and Classification of Urinary Incontinence: Recommendations of the Urodynamic Society. *Neurourology and Urodynamics* 1997; 16:149-151.

⁶ Walsh P et al, editors: *Campbell's Urology* 7th edition W.B. Saunders Company, Philadelphia, 1998, p. 925.

⁷ International Continence Society Committee on Standardisation of Terminology: The Standardisation of Terminology of Lower Urinary Tract Function. *Scand J Urol Nephrol Supplementum* 114, 1988 p. 5-19.

urge incontinence (≥ 5 incontinence episodes per week) and had symptoms of overactive bladder for ≥ 6 months. Thus study 98-TOCR-007 was performed on a select subgroup of all patients with overactive bladder.

Reviewer's comments:

- 1) In the Phase 3 trial, tolterodine ER was demonstrated to be effective only in a select subgroup of overactive bladder patients and only with the 4 mg qAM dose. The Sponsor seeks approval in all subgroups of overactive bladder patients for the 2 mg and 4 mg dose of tolterodine ER.**

2.1 Regulatory History

Pharmacia, Inc. submitted the original _____ for tolterodine IR tablets (Detrol™) to HFD-160, Division of Medical Imaging and Radiopharmaceutical Drug Products, on September 2, 1994. The IND was transferred as a result of the CDER restructuring initiative to HFD-510, Division of Metabolic and Endocrine Drug Products (DMEDP), on November 17, 1995. The IND was transferred to HFD-580, Division of Reproductive and Urologic Drug Products (DRUDP), in June 1996 as a result of the formation of this new division from HFD-510. Notice of the change in sponsor name from Pharmacia, Inc. to Pharmacia & Upjohn Company was submitted on June 26, 1996 and was received on September 19, 1996.

The Detrol™ original NDA 20-771 was submitted on March 24, 1997 and was approved on March 25, 1998. Data regarding a Phase 4 commitment to conduct a multi-dose study in hepatic failure patients with ECG monitoring was submitted on March 24, 1998.

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

On May 14, 1999, notice of fulfillment of all Phase 4 commitments for NDA 20-771 was sent to the sponsor. On August 12, 1999, guidance for studies regarding the Pediatric Rule and Pediatric Exclusivity was provided to the sponsor during a teleconference.

The fourth supplemental submission to NDA 20-771 was SE8-004 (Supplement-Labeling Revision with Clinical Information). It was submitted on December 22, 1999. It presented clinical data from Protocol 98-TOCR-007, which was performed under _____. 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. The Sponsor was sent an approvable action letter pending labeling on October 23, 2000 when no response had been received from the sponsor regarding the Agency revised Package Insert sent to the Sponsor on September 29, 2000. A resubmission containing Sponsor revisions to the proposed label was received on October 27, 2000 and is under review.

The sixth supplemental submission to NDA 20-771 was **SLR-006** (Supplement-Labeling Revision). It was submitted on May 31, 2000 and was approved on October 24, 2000. It added a toll-free number and website address to the carton for complimentary samples of Detrol™ tablets and was submitted as CBE (Changes Being Effected).

The eighth supplemental submission to NDA 20-771 was **SLR-008** (Supplement-Labeling Revision). It 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.

Pharmacia & Upjohn opened _____ for tolterodine extended release capsules on July 14, 1998 with the Phase 1 PK food effect Protocol 98-TOCR-010. A guidance FDA meeting was held regarding the proposed Phase 3 study, Protocol 98-TOCR-007 on August 12, 1998. The sponsor was advised at this meeting:

- Mean volume voided was not an acceptable primary endpoint. Frequency voided and/or number of incontinence episodes would be more appropriate endpoints. The primary efficacy endpoint should be the proposed indication for the label.
- A 15% reduction in dry mouth between tolterodine IR and tolterodine ER was not acceptable; a 25-50% reduction using a visual analog scale was more appropriate.
- An additional 3-month follow-up of approximately 100 patients at 6 months and 50 at one year should be considered for the ER formulation.
- Labeling changes would be based on the study results; statistical as well as clinical differences.

The Sponsor meeting minutes from the August 12, 1998 meeting stated:

- Pharmacia & Upjohn needs to propose what a significant difference [from placebo] would be and in what type of patient. A reduction of two treatments within 20% of each other would be deemed equivalent while a difference of 25-50% would be considered significantly different.

Revisions to Protocol 98-TOCR-007 were made based upon FDA comments and the final sponsor date was October 30, 1998.

Further Protocol 98-TOCR-007 FDA comments were made at an End-of-Phase 2 (EOP2) meeting for NDA 21-228 which took place on November 30, 1998. The sponsor was advised at this meeting:

- Labels will be the same regarding the wording of the indication for all drugs in this class.
- A determination of how many [incontinence] episode changes from baseline are meaningful to the patient is important.
- A clinically meaningful difference might be a 20-25% decrease in weekly incontinence episodes per week.
- Ideally, a clinically significant difference [for reduction in dry mouth between the ER and IM formulations] should be determined prospectively and a separate study should be conducted to confirm that this difference is meaningful to the patients. Alternatively, providing the scientific rationale which supports a 25% reduction in dry mouth as being clinically significant is acceptable.

There were a total of 4 Amendments to Protocol 98-TOCR-007:

Amendment 1: Sponsor date December 7, 1998; Correspondence date January 20, 1999

Amendment 2: Sponsor date January 22, 1999; Correspondence date May 21, 1999

Amendment 3: Sponsor date March 31, 1999; Correspondence date May 21, 1999

Amendment 4: Sponsor date July 2, 1999; Document could not be located in DFS or Document Room. Sponsor was called on August 16, 2000 and confirmed that due to an error, it was never submitted. Amendment 4 was then submitted as Serial Number 040 on August 21, 2000. It was noted upon review that the following new sentence had been inserted into Section 10 STATISTICS 1. Intention to treat population:

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

The sponsor was asked to clarify what was meant by the term "estimation" and provide a listing of patients for which estimations was performed. The sponsor submitted via fax dated September 7, 2000 the clarification that "estimated" meant "calculated" in this case. They also submitted a listing of 16 placebo subjects, 18 tolterodine PR 4 mg qd subjects, and 18 tolterodine IR 2 mg bid subjects who had estimation of micturition data in protocol 98-TOCR-007 performed because the micturition chart diary was completed for less than 5 days.

NDA 21-228 was submitted on February 25, 2000 and received a CDER stamp date of February 28, 2000.

There have been a total of 9 Amendments submitted to NDA 21-228:

Amendment 1: NDA Volume 1.3 of 1.51 Chemistry was resubmitted due to several of the figures on pages 30-66 not printing; Correspondence date March 31, 2000

Amendment 2: Additional Manufacturing Site Information; Correspondence date April 3, 2000

Amendment 3: FDA form 3454 located in the Financial Disclosure section (Item 19) was withdrawn; it had been submitted in error; Correspondence date April 26, 2000

Amendment 4: 4-month Safety Update for Protocol 98-TOCR-007B; Correspondence date June 28, 2000

Amendment 5: Pediatric Study Plan and Proposed Pediatric Study Request; Correspondence date June 28, 2000

Amendment 6: Additional CMC information was submitted; Correspondence date June 30, 2000

Amendment 7: Amendment #4 to protocol 98-TOCR-007 was submitted; Correspondence date August 28, 2000

Amendment 8: Minor Clinical Amendment submitted; Correspondence date October 3, 2000

Amendment 9: Minor Chemistry Amendment; Correspondence date November 3, 2000

Two Final Reports of Phase 3 Trials were submitted to _____ as N135-IM, both with the Correspondence date of July 7, 2000:

Protocol 96-OATA-032: Long-term safety, tolerability and clinical efficacy of tolterodine 2 mg bid. A phase III, open, multinational study for up to two years in patients with detrusor overactivity, symptoms of frequency, urge incontinence and/or urgency.

Protocol 96-OATA-034: Long-term safety, tolerability and clinical efficacy of tolterodine 1 mg bid. A phase III, open, multinational study for up to two years in patients with detrusor overactivity, symptoms of frequency, urge incontinence and/or urgency.

2.2 Clinical Background and Scientific Rationale

Muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells.⁸ The best known member of the muscarinic receptor antagonist drug class is atropine and the actions of most clinically available muscarinic receptor antagonists differ only quantitatively from those of atropine. Muscarinic receptor antagonists have been used therapeutically in ophthalmology, anesthesia, the cardiovascular and central nervous systems, and the gastrointestinal, respiratory, and genitourinary tracts.

Tolterodine is a muscarinic receptor antagonist used for its antispasmodic effect on the bladder. It reduces the activity of the detrusor muscle. Detrusor muscle contractions are mainly mediated through cholinergic muscarinic receptors, of which there are five known subtypes. Bladder smooth muscle cholinergic receptors are mainly of the M-2 variety. However, it is generally felt that the M-3 variety is responsible for involuntary bladder contractions.⁹ Inappropriate detrusor contractions can lead to a sense of urgency, which is a sudden, strong desire to urinate. Increased urgency can lead to urinary frequency and urge incontinence.

Overactive bladder is characterized by its symptoms of urinary frequency, urinary urgency and in many cases urge incontinence. The most bothersome symptom for patients and with the highest consequences to daily life is urge incontinence. Tolterodine immediate release tablets (Detrol™)

⁸ Hardman JG, Editor et al, *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill New York, Ninth Edition, 1996, p. 148.

⁹ Wein AJ and Rovner ES. The Overactive Bladder: An Overview for Primary Care Health Providers. *Int J Fertil* 44(2), 1999 p. 64.

in a bid dosage regimen have been approved for the treatment of overactive bladder in the United States and for unstable bladder in the European Union countries. The major competitor for tolterodine is oxybutynin chloride (Ditropan™) and an extended release (ER) formulation (Ditropan™ XL) by ALZA was approved on December 16, 1998. In this NDA, Pharmacia & Upjohn submit their extended release formulation for tolterodine.

2.3 International Marketing Experience

Tolterodine IR tablets in a bid dosage regimen have been approved for the treatment of overactive bladder or unstable bladder in 47 countries, including the United States and the European Union. The International Birthdate for tolterodine IR is September 5, 1997. Tolterodine IR was approved in the European Union Countries on December 23, 1997 for unstable bladder. It was approved in the US (NDA 20-771) on March 25, 1998 for overactive bladder.

Per NDA 20,771 Annual Report Y-002 dated May 12, 2000, the total quantity of Detrol™ distributed from January 1, 1999 through December 31, 1999 was:

Domestic	██████████	boxes or bottles of 1.0 and 2.0 mg tablets
International	██████████	blisters or bottles of 0.7, 1.0, and 2.0 mg tablets

As of February 28, 2000, tolterodine ER capsules had not yet been registered anywhere in the world.

3.0 SUMMARY OF NDA 21-228

3.1 Summary of Controlled Trials

The Clinical/Statistical Data section of NDA 21-228 contains the study reports of two controlled studies: 97-TOCR-002 and 98-TOCR-007 with the corresponding extension study 98-TOCR-007B.

Study 97-TOCR-002 was a multicenter, multinational, randomized, double-blind, double-dummy, cross-over, incomplete block, placebo controlled, dose-effect and dose-finding Phase 2 study of tolterodine ER 2, 4, 6, and 8 mg capsules compared to tolterodine IR 2 mg bid and placebo in patients with overactive bladder. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruba J. Chatterjee, Ph.D. dated 11/21/00 pages 11-14 and Attachment III pages 27-29)

Study 98-TOCR-007 was a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency and urge incontinence. The study had three equally sized arms: tolterodine ER capsules 4 mg qAM, tolterodine IR tablets 2 mg bid, and placebo. The study was comprised of three periods: a 1- to 2-week wash-out/run-in period, a 12-week treatment period, and a 1-week follow-up period. The primary efficacy endpoint was the change in number of incontinence

episodes per week from baseline to week 12. A total of 1529 patients were randomized to treatment at 167 sites in 14 countries.

Study 98-TOCR-007B was an open-label, uncontrolled, multicenter, multinational, non-randomized Phase 3 trial in adult patients with urinary frequency and urge incontinence. Patients who fulfilled all eligibility criteria before randomization and completed the original protocol, 98-TOCR-007, were invited to participate in this continuation trial. They received tolterodine ER capsules 4 mg qAM without breaking the blind for the original trial. The study was comprised of two periods: a 12-month treatment period and a 1-week follow-up period. The primary endpoints were safety variables and were assessed at a telephone contact after one month of treatment and at four Visits (after 3, 6, 9, and 12 months of treatment). The secondary endpoints were efficacy variables and were assessed at two Visits (after 3 and 12 months of treatment). The 4-month Safety Update submitted on June 28, 2000 contained an interim report of this trial with a cut off date of April 30, 2000. As of this date, 135 patients had been treated for 12 months and 1072 patients had been treated for 6 months.

3.2 Summary of Uncontrolled Trials

The Clinical/Statistical Data section of this application contains the study reports of five uncontrolled clinical trials submitted in this application:

- **97-TOCR-001**; phase 1, **single-dose**, randomized, cross-over, open, fed and fasted bioavailability study of tolterodine ER 8 mg capsules and tolterodine ER 8 mg tablets to characterize the **pharmacokinetic profiles**, to determine the *in vivo* dissolution rates, to study the food effects on bioavailability, and to study salivation effects in 10 healthy volunteers. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruva J. Chatterjee, Ph.D. dated 11/21/00)
- **97-TOCR-003**; phase 1, **single-dose**, randomized, cross-over, open, **pharmacokinetic study** of 4 batches of tolterodine ER capsules with different dissolution rates *in vitro*, compared to a tolterodine oral solution in 10 healthy volunteers. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruva J. Chatterjee, Ph.D. dated 11/21/00 pages 14-17)
- **98-TOCR-005**; phase 1, **single-dose**, randomized, crossover, open, **pharmacokinetic study** of 4 batches of tolterodine ER capsules with different dissolution rates *in vitro* (II), compared to a tolterodine oral solution in 16 healthy volunteers. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruva J. Chatterjee, Ph.D. dated 11/21/00 pages 14-17)
- **98-TOCR-006**; phase 1, **multiple-dose**, randomized, crossover, open, **pharmacokinetics and pharmacodynamics** of tolterodine ER capsules in comparison with tolterodine IR tablets in 19 healthy volunteers. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruva J. Chatterjee, Ph.D. dated 11/21/00 pages 8-14 and Attachment II pages 26-27)
- **98-TOCR-010**; phase 1, **single-dose**, randomized, crossover, open, **effect of food on the bioavailability** of tolterodine ER capsules and compared to tolterodine IR tablets in 17 healthy volunteers. (See Clinical Pharmacology & Biopharmaceutics Review by Dhruva J. Chatterjee, Ph.D. dated 11/21/00 pages 5-8 and Attachment I pages 25-26)

4.0 CLINICAL TRIAL 98-TOCR-007: Clinical efficacy and tolerability/safety of tolterodine prolonged release capsules and tolterodine immediate release tablets vs

placebo. A randomized, double blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder.

4.1 Objectives

The primary objective of this trial was to evaluate the effects of tolterodine extended release (ER) capsules 4 mg qAM and tolterodine immediate release (IR) tablets 2 mg BID on incontinence episodes in adult subjects with urge incontinence over a 12-week treatment period, as compared with placebo.

The secondary objectives were to compare efficacy and tolerability/safety of tolterodine ER capsules 4 mg qAM and tolterodine IR tablets 2 mg BID with placebo in adult subjects with urge incontinence over a 12-week treatment period.

4.2 Design and conduct of the trial

This was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency, urge incontinence, and overactive bladder symptoms for ≥ 6 months. The study had three equally sized arms: tolterodine ER capsules 4 mg qd, tolterodine IR tablets 2 mg bid, and placebo.

The study was comprised of three periods: a 1- to 2-week washout and run-in period, a 12-week treatment period, and a 1-week follow-up period. The expected duration of subject participation was 14 to 15 weeks. The washout period could be omitted for subjects that had no drug treatment for overactive bladder, bladder training or electrostimulation or anticholinergic drugs for the 14 days prior to randomization. All subjects participated in a minimum of a 1-week run-in period during which they completed micturition histories to confirm eligibility. The wash-out/run-in period was extended if the subject had a symptomatic urinary tract infection during the wash-out/run-in period or at the day of Visit 2. In such a case, the subject received treatment for the UTI and a new appointment for Visit 2 was given.

Reviewer's comments:

- 1) Since neither a urinalysis nor a urine culture were scheduled laboratory tests to be obtained on subjects during the wash-out/run-in period, it would be expected that asymptomatic patients with UTIs were included in this trial. This could bias the study population. Confirming that a patient has a normal urinalysis is recommended before initiating treating for overactive bladder.¹⁰ However in this trial, a similar percentage of subjects would be expected to have asymptomatic urinary tract infections at Visit 2 and at Visit 4. It is not expected that the efficacy data would be affected.

Baseline assessments were collected or made at Visit 2, which was 1 day prior to treatment initiation. A baseline cough provocation test was performed on female patients clinically suspected of having stress incontinence, unless they had had a complete urodynamic investigation within 14 days prior to randomization. The cough provocation test was performed with the subject in position for gynecological examination. The bladder volume was confirmed

¹⁰ Abrams P and Wein AJ. The Overactive Bladder: A Widespread and Treatable Condition, Stockholm, Sweden: Erik Sparre Medical AB; 1998: p. 1-60 as quoted in Hoffman E. Overactive bladder: Diagnosis of a hidden disorder. *Contemporary OB-GYN*. Summer 2000 Supplement: p. 16

by ultrasound to exceed 100 ml, and subsequently the subject was asked to cough vigorously. If an immediate loss of urine was confirmed, the clinical diagnosis of stress incontinence was made and the subject was excluded from the trial. In Protocol Amendment #3, the subject's position during the cough provocation test was changed to supine.

Micturition charts and QoL questionnaires were completed at baseline and at end of treatment. A pad weight test was performed in centers in the United States and Australia at baseline and at end of treatment. Eligible patients who completed the 12-week treatment period were invited to participate in an open label long-term follow-up study that consisted of treatment with tolterodine ER 4 mg qd for 12 months (98-TOCR-007B).

Pharmacia & Upjohn (Stockholm, Sweden) planned 98-TOCR-007. Centers were monitored by local Pharmacia & Upjohn monitors. Pharmacia & Upjohn Clinical Supply Logistics distributed treatments to each participating Pharmacia & Upjohn Market Company, which were responsible for distribution to local pharmacies or investigators.

4.3 Study population

It was planned that the trial would enroll 1350 subjects at 150 investigator sites with 9 subjects per investigator.

A total of 1529 subjects (North American=804, European=608, and Australian/New Zealand=117) were randomized to tolterodine ER (n=507), tolterodine IR (n=514) or placebo (n=508). The study was conducted in a total of 167 sites in 14 countries. The sites were in North America (Canada=10, United States=64), in Europe (Austria=7, Belgium=7, France=9, Germany=15, Ireland=5, Italy=7, Netherlands=12, Norway=5, Russian Federation/Ukraine=5, United Kingdom=14) and in Australia=4/New Zealand=3. Recruitment per center ranged from 1 patient (9 centers) to 40 patients (1 center) with an average of 9 subjects per investigator. Fifty-six sites (34%) enrolled 5 or less subjects. European sites had lower patient recruitment (average 7.1 subjects/site) than North American (average 10.9 subjects/site) or Australian/New Zealand sites (average 16.7 subjects/site).

The first patient was recruited on February 19, 1999 and the last patient completed all study-related assessments on November 8, 1999. The last date a patient was on study drug was October 31, 1999.

4.3.1 Demographics

Demographic data collected on subjects prior to randomization included date of birth, sex, weight, height, and ethnic origin. The study population was 81% female, 19% male, 95% White and 3.6% Black. The mean subject age was 60 years.

Reviewer's comments:

- 1) **Randomized subjects were overwhelmingly Caucasian. Sex, race and age characteristics were similar in the three treatment groups and in the ITT and PP populations.**

- 2) In the United States, several population studies have found a 20 to 40% higher prevalence of urinary incontinence among white women than among African American women.^{11,12,13} However this difference is related to the apparent greater prevalence of stress incontinence among white women.¹⁴ African Americans were twice as likely to have urge incontinence as whites (57% versus 28%).¹⁵ The Clinical Trials section of the labeling should state that the majority of the 98-TOCR-007 study population was Caucasian (95 %).

4.4 Inclusion and exclusion criteria (includes the one amendment change to the original Exclusion criteria #1)

Inclusion criteria:

- 1) Male or female subjects aged ≥ 18 years.
- 2) Subjects with urinary frequency (on average ≥ 8 micturitions per 24 hours) and urge incontinence (≥ 5 incontinence episodes per week) as verified in the micturition chart before randomization.
- 3) Subjects with symptoms of overactive bladder for ≥ 6 months.
- 4) Subjects able and willing to correctly complete the micturition charts.
- 5) Subjects capable of understanding and having signed the informed consent form after full discussion of the research nature of the treatment and its risks and benefits.

Exclusion criteria:

- 1) Subjects with stress incontinence as determined by the investigator and for a female subject confirmed by a cough provocation test according to appendix 4.
- 2) Subjects with an average volume voided > 200 ml urine per micturition as verified in the micturition chart before randomization.
- 3) Subjects with a total daily volume of urine > 3000 ml as verified in the micturition chart before randomization.
- 4) Any condition which in the opinion of the investigator makes the subject unsuitable for, or with contraindication for inclusion, i.e. uncontrolled narrow-angled glaucoma, urinary retention and gastric retention.
- 5) Subjects with significant hepatic or renal disease, defined as twice the upper limit of the reference ranges regarding serum concentrations of AST, ALT, ALP or creatinine.
- 6) Subjects with symptomatic acute urinary tract infection (UTI) during the run-in period, or recurrent UTIs defined as treated for symptomatic UTI > 5 times in the last year.
- 7) Subjects with diagnosed interstitial cystitis, uninvestigated hematuria or clinically significant bladder outlet obstruction.

¹¹ Thom DH et al. Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life. *Obstet Gynecol.* 1997; 90: 983-989.

¹² Brown JS et al. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. *Obstet Gynecol.* 1999; 94:66-70

¹³ Fultz NH et al. Prevalence and severity of urinary incontinence in older African American and Caucasian women. *J Gerontol Biol Sci Med Sci.* 1999; 54: M299-M303.

¹⁴ Thom DH et al. Overactive bladder: Epidemiology and impact on quality of life. *Contemporary OB/GYN.* Summer 2000 Supplement; 9.

¹⁵ Bump RC. Racial comparisons and contrasts in urinary incontinence and pelvic organ prolapse. *Obstet Gynecol.* 1993; 81: 421-425.

- 8) Subjects treated within the 14 days preceding randomization, or expected to start treatment during the trial with
 - any anticholinergic drug other than trial drug according to randomization
 - any drug treatment for overactive bladder. Estrogen treatment started more than 2 months prior to randomization was allowed.
- 9) Subjects on an unstable dosage of any drug with anticholinergic side effects, or expected to start such treatment during the trial.
- 10) Subject on treatment with potent CYP3A4 inhibitors, such as macrolide antibiotics (erythromycin, clarithromycin) or antifungal agents (ketoconazole, itraconazole, miconazole), or expected to start such treatment during the trial.
- 11) Subjects who have received any electrostimulation or bladder training within the last 14 days before randomization, or who are expected to start such therapy during the trial period.
- 12) Subjects with indwelling catheter or the practicing of intermittent self-catheterization.
- 13) Any other investigational drug within 2 months preceding randomization.
- 14) Subjects who are pregnant or nursing.
- 15) Sexually active female subjects of childbearing potential not using reliable contraceptive methods at least 3 months prior to randomization, during the entire trial period and for 1 month thereafter. Reliable contraceptive methods are intrauterine devices (IUD), contraceptive pills of combination type, hormonal implants and injectable contraceptives.

Reviewer's comment:

- 1) Regarding Exclusion #6, subjects were not excluded if they experienced symptomatic acute UTI during their first run-in period. The subjects were treated for the UTI and then repeated their run-in period.
- 2) Regarding Exclusion #7, screening urinalysis were not performed as part of the study, thus it would be unlikely for uninvestigated hematuria to be diagnosed during the screening or admission periods.
- 3) Regarding Exclusion #8, subjects were not withdrawn if estrogen treatment was changed or stopped during the treatment period.
- 4) Regarding Exclusion #8-10, taking a prohibited concomitant medication was considered a protocol deviation and not a protocol violation. Subjects were not withdrawn from the trial unless they violated Exclusions #4, 5, 14 or 15 (per Vol. 26/51 pg. 57). By comparing the line listings in Vol. 34/51 Appendix 13-Withdrawn Subjects with the line listings in Vol. 34/51 Appendix 14-Protocol Deviations, a total of 11 placebo and 5 Tolterodine ER subjects were identified who took a prohibited concomitant medication during the trial. Of these 16 subjects, only one subject (#3114-placebo) was withdrawn from the trial. Subject #3114 took the prohibited anticholinergic medication, Atrovent and was withdrawn after 26 days of treatment on August 7, 1999. Subject #3114 was started on Ditropan beginning August 8, 1999. The remaining 15 subjects who took a prohibited concomitant medication were not withdrawn and six were taking Atrovent (per Vol. 25/51 Appendix 19 pg.1-226).

4.5 Procedures

4.5.1 Screening period

During the 7-14 day washout and run-in period which began with Visit 1, the study design and purpose was explained to the volunteers and they were assessed for eligibility. Written informed

consent was obtained. Demographic data and vital signs were obtained. The history of any prior treatment(s) for overactive bladder and/or concomitant medication was elicited. Blood samples for clinical chemistry, hematology, and CYP2D6 genotyping were obtained. A urine pregnancy test was performed locally in women of childbearing potential. A measuring jar, micturition chart and instructions were given to all subjects. Every incontinence episode and every micturition associated with a sensation of urgency were to be recorded at the times they occurred for 7 consecutive days prior to Visit 2. In addition for at least 2 complete days, the volume voided (in milliliters) for every micturition, and every pad used were to be recorded at the times they occurred. In centers in the United States and Australia, approximately 375 subjects who had previously used pads were instructed to collect all pads used over 2 days prior to Visit 2 for the pad weight test. They received standardized pads, zip-lock bags, and a collection bag along with detailed instructions for the pad weight test.

Reviewer's comment:

- 1) Studying only patients who had previously used pads was reasonable, however it would bias the pad weight subgroup toward the more severe urge incontinence patients. This point became irrelevant when the sponsor opted to delete analyzing the pad weight test data.**

4.5.2 Admission period

The admission period began at Visit 2 and occurred after results of routine laboratory tests qualified the patient for trial participation. The micturition chart and any pads for the pad weight test were collected. Pads were counted and weighed on standardized scales. The investigator together with the subject resolved any micturition chart ambiguities. Eligibility was again determined, which included investigator assessment of the completed micturition charts. The investigator calculated the number of micturitions and incontinence episodes, mean volume voided per micturition, and the total daily urine volume. Concomitant medication information was obtained. Concurrent disease or symptoms present at the day of Visit 2 and their intensity was obtained. The investigator assessed the subject's perception of bladder condition and urgency. The subject completed the two QoL assessments: King's Questionnaire and SF-36. Patients in the Netherlands, Norway, Belgium (Flemish speaking), Russian Federation and Ukraine were exempt from filling out the King's Health Questionnaire because validated translations were not available in the appropriate languages.

ECGs in a subgroup of subjects ≥ 65 years in the United States (planned $n=90$) were obtained. If female subjects were suspected to have stress incontinence as determined by the investigator, they underwent the cough provocation test to confirm the diagnosis. Five weeks after enrolling the first patient, the cough provocation test was changed in protocol Amendment 3 to be performed in the standing rather than supine position.

Reviewer's comment:

- 1) To confirm subject eligibility, it would have been optimal for each female subject to undergo the cough stress test. However it is reasonable in a Phase 3 trial to perform the test only in female subjects suspected of stress incontinence, as would likely occur in clinical practice.**

- 2) **It is unknown whether or not a cough stress test was performed and what the results were for any enrolled subject. The trial's Case Report Form (CRF) did not collect this data.**

The subjects were then randomized in a block size of six and drug dispensed. Each subject received three bottles, with different content, in a box containing sufficient study medication for 4 weeks of treatment plus 7 surplus doses per bottle. One bottle contained 35 capsules of tolterodine ER or its placebo and was marked "morning dose". The other 2 bottles each contained 35 tablets of tolterodine IR or its placebo; one was marked "morning dose" and one was marked "evening dose". Subjects were instructed to take one capsule and one tablet each morning from the bottles labeled "morning dose" and one tablet each evening from the bottle labeled "evening dose" beginning the day after Visit 2. There were no dosing restrictions with regard to food or relation to daily activities.

4.5.3 Treatment period

Subjects were seen for two visits (Visit 3 and Visit 4) during the treatment period.

Visit 3 occurred 28 ± 4 days after Visit 2. At Visit 3, concomitant medication and Adverse Event information was obtained. Micturition charts were dispensed with instructions to complete for 7 consecutive days before the last dose of study medication. Those subjects who had received pads at Visit 1 again received standardized pads at Visit 3 with the instruction to collect each used pad for 2 days before the last dose of study medication. Drug was returned and two boxes of drug were dispensed. The investigator verified subject compliance by capsule/tablet count.

Visit 4 occurred 84 ± 4 days after Visit 2 or upon subject withdrawal from the trial. At Visit 4, concomitant medication and Adverse Event information was obtained. The investigator assessed the Subject's perception of urgency, Subject's perception of treatment benefit, and Subject's perception of urgency. The QoL assessments (King's Questionnaire and SF-36) were completed. The micturition chart and pads were collected. Drug was returned. The investigator verified subject compliance by capsule/tablet count. Clinical chemistry and hematology blood samples were obtained. Urine pregnancy testing was performed locally according to country specific requirements for female subjects of childbearing potential. ECGs were obtained in the subgroup of ≥ 65 -year-old subjects who had ECGs performed at Visit 2 in United States centers. Pads were collected, counted and weighed in the subgroup of subjects who had participated in the pad weight test at Visit 2 in United States and Australian centers.

Reviewer's comment:

- 1) **"During-treatment" efficacy diary data was collected only on the 7 days prior to the last dose of medication. The reviewer considered it unlikely that the prematurely withdrawn subjects (12.2% of all subjects in the study) would have collected "during-treatment" efficacy diary data before withdrawing. In Vol. 26/51 p. 57 it was stated that if possible any prematurely withdrawn patient was to have completed the micturition chart for the last 7 days on study medication. By analyzing the efficacy diary data, the reviewer determined that only 4 of the 68 placebo and 9 of the 57 tolterodine ER prematurely withdrawn subjects completed at least 5 "during-treatment" diaries. 82% of prematurely withdrawn tolterodine ER subjects (n=47) completed no "during-**

treatment” diaries, so it is unlikely that diary data from prematurely withdrawn patients biased the efficacy data results.

4.5.4 Post-Treatment period

Visit 5 occurred one week after treatment for post-treatment follow-up. At this visit or telephone contact, concomitant medication and Adverse Event information was obtained. Unresolved adverse events that were judged by the investigator as related to study medication were to be followed until resolved or assessed as chronic or stable.

4.6. Evaluation criteria

4.6.1 Efficacy

The **primary efficacy variable** was the mean number of incontinence episodes per week.

The **primary efficacy endpoint** was the change in mean number of incontinence episodes per week as determined from the micturition charts taken at baseline and at the end of treatment (week 12 or withdrawal).

The **secondary efficacy variables** were the mean number of micturations per 24 hours, mean volume voided per micturation, number of pads used per 24 hours, subject’s perception of bladder condition, subject’s perception of urgency, subject’s perception of treatment benefit, and QoL variables. Data on an additional secondary efficacy variable (proportion of micturations associated with urgency) were collected but not analyzed due to sponsor concerns that there were misconceptions regarding the term urgency that led to improper completion of the micturition charts. Data on an additional secondary efficacy variable (mean urine weight per incontinence episode) were collected but not analyzed due to technical difficulties with the pad weight test preventing accurate data from incomplete or unreliable information on the weight of the dry pad. Additional secondary efficacy variables (antimuscarinic effects of dry mouth, constipation, and vision abnormalities including accommodation abnormalities using visual analogue scales) were deleted in Amendment 1.

The **secondary efficacy endpoints** were changes from baseline to the end of treatment (week 12 or withdrawal):

- Mean number of micturations per 24 hours (from the micturition charts)
- Mean volume voided per micturation (from the micturition charts)
- Number of pads used per 24 hours (from the micturition charts)
- Proportion of micturations associated with urgency (from the micturition charts-data not analyzed by sponsor)
- Mean urine weight per incontinence episode (from the pad weight test subgroup-data not analyzed by sponsor)
- Subject’s perception of bladder condition
- Subject’s perception of urgency
- Subject’s perception of treatment benefit (assessed only at end of treatment)
- QoL scores

Reviewer’s comments:

- 1) **Sponsor did not correlate subject's change in perception of bladder condition or urgency with subject's perception of treatment benefit. This resulted in some subjects reporting a worsening of bladder condition on treatment while simultaneously reporting a positive treatment benefit. For example, subject #1097 (on placebo treatment) reported some moderate bladder problems at start of treatment, severe bladder problems at end of treatment, and much benefit from treatment.**
- 2) **Sponsor should have followed the prespecified protocol analysis plan, analyzed the pad weight data, and discussed the percentage of data felt to have be accurate. It is well known that pad tests are fraught with difficulties such as subject noncompliance, need to carefully preweigh all pads used, and need to adjust for weight of any non-urine fluid on pad.**
- 3) **Sponsor should have followed the prespecified protocol analysis plan, analyzed the proportion of micturations associated with urgency, and discussed the percentage of data felt to be accurate.**

Regarding the efficacy endpoints calculated from the micturition chart:

- Volumes voided per micturition and numbers of pads used were averaged for a minimum of 2 days
- All other chart variables were averaged for a minimum of 5 completed days.

4.6.2 Safety

The **safety variables** were adverse events, withdrawals, laboratory variables, and in selected United States centers ECG QT, QTc and QT dispersion.

The **secondary safety endpoints** were changes from baseline to the end of 12 weeks of treatment in:

- Proportion of subjects with adverse events grouped according to WHO preferred term
- Proportion of withdrawn subjects
- Hematology and clinical chemistry laboratory results
- QT, QTc and QT dispersion on ECG for subjects ≥ 65 years of age in selected United States centers

4.7 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. Subjects who were found to violate the exclusion criteria #4, 5, 14 or 15 regarding contraindicated conditions, significant hepatic or renal disease, pregnancy or lactation, or lack of effective birth control (females of childbearing potential) were immediately withdrawn from the trial for reasons of subject safety. For any prematurely withdrawn subject, all assessments that were related to Visit 4 were to be performed within 3-to-9 hours after the last dose of study medication, if possible. Also, if possible, any prematurely withdrawn subject was to have completed the micturition chart for the last 7 days on study medication.

A total of 187 (12.2%) subjects were prematurely withdrawn from the study for any reason. An adverse event (AE) was the most common reason subjects were prematurely withdrawn (47%).

Similar percentages of subjects were prematurely withdrawn and for similar reasons in the three arms of the study (See Table #1).

Table #1-Subjects Prematurely Withdrawn from Study
(Created by MO from Table 4 Vol. 26/51 pg. 76)

	Total Number of Subjects	Number Withdrawn (% of total number)	Number due to AEs (% of total number)
Tolterodine ER	507	57 (11.2%)	27 (5.3%)
Placebo	508	68 (13.4%)	33 (6.5%)
Tolterodine IR	514	62 (12.1%)	28 (5.4%)
Total	1529	187	88

Per the protocol (Vol. 26/51 p.215), subjects who completed the trial according to the protocol i.e., no major violation from the inclusion/exclusion criteria, compliance and have recorded data form both baseline and 12 weeks visit were included in the PP analysis. Unfortunately, the major violations from the inclusion/exclusion criteria were not prespecified in the protocol. In the Final Study Report (Vol. 26/51 p. 77 and Vol. 34/51 p. 21-33), the Sponsor defined these major protocol violations as:

- Randomized but did not take any study medication. One placebo and 2 tolterodine ER subjects were randomized but did not take study medication.
- <4.5 incontinence episodes per week at baseline. Twelve placebo and 13 tolterodine ER subjects reported less than 4.5 incontinence episodes per week at baseline.
- Missing micturition chart (MC). At Visit 2, one placebo and one tolterodine ER subjects had a missing MC. At Visit 4, 64 placebo and 47 tolterodine ER subjects had a missing MC.
- Incomplete micturition chart (defined as less than 5 days completed for 24 hours, or completed after or at first dose of trial medication or completed after last dose of trial medication. At Visit 2, 15 placebo and 10 tolterodine ER subjects had an incomplete MC. At Visit 4, 27 placebo and 25 tolterodine ER subjects had an incomplete MC.
- Invalid micturition chart (defined as symptomatic UTI during the days of completion). At Visit 2, no placebo and no tolterodine IR subjects had UTIs. At Visit 4, 11 placebo and 8 tolterodine IR subjects had UTIs
- Documentation of missing >25% of the prescribed treatment medication (7 placebo and 12 tolterodine ER subjects) or missing compliance data (18 placebo and 9 tolterodine ER subjects)

A total of 360 (23.5%) subjects had at least one major protocol violation and should have been excluded from the PP analysis. 288 of the 360 subjects (80%) with at least one major protocol violation had a missing, incomplete, or invalid micturition charts. Overall, there were similar numbers of subjects in all three arms of the study having major protocol violations and similar percentages in all three arms for any particular major protocol violation.

**Table #2-Subjects with Major Protocol Violations
(Created by MO from Table 5 Vol. 26/51 pg. 77)**

	Total Number of Subjects	Number Subjects with Major Protocol Violations (% of total number)	Number due to missing, incomplete, or invalid micturition charts
Tolterodine ER	507	109 (21.5%)	88
Placebo	508	134 (26.4%)	108
Tolterodine IR	514	117 (22.8%)	92
Total	1529	360 (23.5%)	288

Reviewer's comments:

- 1) It is concerning that the primary efficacy endpoint was taken from the micturition charts and 288 of the 1529 subjects (18.8%) had missing, incomplete, or invalid micturition charts. However similar numbers of subjects in each of the three arms had missing, incomplete, or invalid micturition charts (see Table #2).
- 2) The site monitors should have noticed the micturition chart inadequacies and reeducated the sites. However the rapid trial enrollment and small total numbers of subjects at many sites may have prevented significant improvement due to reeducation from occurring.
- 3) A definition of major protocol violations was not found in the trial protocol or amendments. The definition of major protocol violations should have been prespecified in the protocol.
- 4) I would have included as major protocol violators any subject who failed to meet the inclusion criteria of having an average of ≥ 8 micturitions/24 hours. A total of 135 subjects (8.8% of randomized subjects) reported less than 8 micturitions/24 hours at baseline.
- 5) The protocol inclusion criterion was ≥ 5 incontinence episodes per week, yet a major protocol violator criteria was < 4.5 incontinence episodes per week. It is unclear why < 5 incontinence episodes per week was not selected as a major protocol violator criteria.
- 6) There was inconsistency regarding whether concomitant use of a prohibited medication excluded a subject from the PP population. The concomitant use of prohibited medications (11 placebo and 5 tolterodine ER subjects) was listed (Table 5 Vol. 26/51 pg 77) as a major protocol violation, however it was not listed (Vol. 26/51 pg 76) in the discussion of major protocol violations that could affect the evaluation of treatment. Review of the data determined that subject using a prohibited medication was excluded from the PP population.

Five patients were prematurely unblinded during the study. Site 065 (Dr. Annik Mombet in Paris, France) accidentally unblinded two (one on placebo and one on tolterodine IR) of the 7 subjects enrolled at the site. Site 220 (Dr. Alan Garely in Great Neck, NY) unblinded two of the 23 subjects enrolled at the site (one on tolterodine ER due to a nonserious adverse event and one on tolterodine IR due to a subinvestigators wish to offer other treatment option after withdrawal). Site 170 (Dr. Robert Freeman in Devon, United Kingdom) unblinded one (on tolterodine ER) of the 17 subjects enrolled at the site after an overdose by patient's daughter.

4.8 Protocol Amendments

4.8.1 Protocol Amendment #1

- ~~Visual Analogue Scales were deleted since they had not been validated to measure antimuscarinic effects.~~
- Pad weight test was changed to being performed in a subset of the trial population; it was changed to being performed in United States centers on subjects who have previously used incontinence pads.
- Hematology laboratory safety assessments were added.
- Exclusion criteria was changed that cough provocation test was only for female subjects.

4.8.2 Protocol Amendment #2

- Pad weight test was changed to being performed in Australian centers, as well as in United States centers.
- King's Health Questionnaire completion was deleted for subjects in the Netherlands, Norway, or by Flemish subjects in Belgium since it is not available in Dutch, Norwegian, or Flemish.

4.8.3 Protocol Amendment #3

- Cough Provocation test was changed to being done in the standing position, instead of the supine position.

4.8.4 Protocol Amendment #4

- Five centers in Russian Federation and Ukraine were added.
- Statistical and analytical plans were changed in response to suggestions from the FDA. An ANOVA replaced the t-test
- King's Health Questionnaire completion was deleted for subjects in the Russian Federation or Ukraine since it is not available in Russian.
- Subgroup analyses on micturition variables with respect to sex and races were 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" was added to the Intention-to-treat population.

Reviewer's comments:

- 1) It was initially unclear exactly how and why the micturition variables in the ITT population would be estimated. In a fax dated September 7, 2000, the sponsor clarified that the term "estimation" referred to using less than five complete days of micturition chart diaries to calculate a week of values. The sponsor also explained how the "estimations" were performed and provided a list of subject numbers who had estimations performed.

4.9 Efficacy analyses

4.9.1 Statistical Methods

The Final Report of the Trial stated that sample size was calculated on the primary efficacy variable to detect a mean difference of 4.2 incontinence episodes per week between tolterodine ER and placebo and assumed a standard deviation of 18.2 (Vol. 26/51 pg. 73). It also stated that in the protocol (Vol. 26/51 pg. 216) the decimal was incorrectly not given for the mean

difference, i.e. 4 was mentioned in the protocol text but 4.2 was used for the calculation. In Appendix 23, the sponsor stated that the sample size was based on "a minimum difference worth detecting of four incontinence episodes" per week (Vol. 48/51 pg. 11). The sample size was adjusted for an expected dropout rate of 20%. No interim analysis was performed.

Reviewer's comments:

1) Sample size calculations were based on reasonable assumptions as confirmed by the trial results:

- **For the trial's ITT population, the mean difference between tolterodine ER and placebo subjects was 4.8 incontinence episodes per week. The trial results were close to the expected mean difference of 4.2 incontinence episodes per week.**
- **For the trial's ITT population, the standard deviation was 15.4 for placebo and 17.8 for tolterodine ER subjects regarding the primary efficacy variable change from baseline to week 12. The expected standard deviation was 18.2.**
- **A total of 12.2 % of subjects were prematurely withdrawn from the trial. The expected drop out rate was 20%.**

It was planned to use the t-test for the primary efficacy variable to test the null hypothesis unless assumption of normal distributed data was violated. If that was the case, the Wilcoxon rank sum test was to be used. Adjustment for multiple tests were to be made according to Bonferroni, i.e. each test would be made with a 2.5% significance level to satisfy an overall significance level of 5%. If the mean number of incontinence episodes/week was greater than 168 (>24 incontinence episodes/24 hours), it was truncated at 168 episodes/week (24 episodes/24 hours). Results were also presented as change in mean number of incontinence episodes/24 hours.

For secondary efficacy variables, 95% confidence intervals were planned to be calculated for mean change from baseline to week 12 between the treatment groups. Subgroup analyses of micturition variables were performed for the ITT population based on gender, age (<65 years, ≥65 years), race, and metabolizer type (extensive, poor).

Three populations were to be used for efficacy analyses per the protocol:

- **Intent-to-treat (ITT) population-included all randomized subjects. The primary analysis was on the ITT population. Missing values at week 12 were substituted with the last value carried forward (baseline value). Missing baseline values were substituted with the last value carried backward (week 12).**
- **Observed cases-all subjects who have recorded data from both baseline and 12 weeks visit.**
- **Per-protocol (PP) population-included all subjects who completed the trial according to the protocol (i.e., had no major violation of the inclusion/exclusion criteria, were compliant, and had data recorded for both baseline and week 12). Analyses on the PP population were supportive data.**

There were several changes in the planned analyses made prior to breaking the blind:

- **Non-parametric methods were to be used if the assumptions of normality was violated, however it was decided that the parametric analysis would be made as primary analysis but a non-parametric analysis was also to be made which would be considered as a supportive analysis**

- The definition of the Per-Protocol population was changed and withdrawn subjects were also included if the patient completed the micturition chart for Visit 4 and all other criteria for Per-Protocol were fulfilled. 12% of subjects in study were prematurely withdrawn.
- Two secondary efficacy variables were not analyzed: the mean urine weight/incontinence episode and the proportion of micturitions associated with urgency.
- On July 2, 1999 in Amendment 4, analysis methods were changed for the ITT population to: If micturition chart diaries were not completed according to the protocol, the estimations of the micturition variables were based on the available data.

The primary efficacy endpoint was analyzed by ANOVA, which included treatment, country, and treatment-by-country factors. Bonferroni's method was used to adjust for multiple testing (tolterodine ER vs placebo and tolterodine IR vs placebo, $\alpha=0.025$). The magnitude of treatment effect for each comparison was determined by the respective 97.5% confidence interval based on the least square means from the ANOVA. The similarity in efficacy between tolterodine ER and IR formulations was described using a 95% confidence interval. Secondary variables were evaluated using 95% confidence intervals for the difference between tolterodine ER and placebo and for tolterodine IR and placebo.

Reviewer's comments:

- 1) **The observed cases analyses was omitted from the study final report. The observed cases analyses were requested from the sponsor and were submitted to NDA 20-771/S-004 Amendment No. 1 dated May 5, 2000. No significant differences were noted in comparing the observed cases analyses with the ITT and PP analyses for the tolterodine ER and placebo patients.**
- 2) **"During-treatment" diary data was obtained only for the seven days prior to last study medication dose. This necessitated carrying forward baseline values to substitute for missing "during-treatment" values and carrying backward "during-treatment" values to substitute for missing "pre-treatment" values. It penalized the sponsor by making it more difficult for the sponsor to demonstrate a treatment effect. This problem would have been minimized if additional "during-treatment" diary data had been collected, e.g., 7 days of diary data collected during every 28 days of treatment.**
- 3) **In 98-TOCR-007, one subject had no efficacy data for any of the visits and was considered missing in the efficacy analyses (Vol. 26/51 pg. 83), however Appendix 15 stated no subjects were excluded from the efficacy analysis (Vol. 34/51 p. 40).**

4.9.2 Efficacy Results

4.9.2.1 ITT Population Efficacy Results

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.1-23.3 incontinence episodes per week. However all treatment arms had a very wide range of 0 to 168 incontinence episodes per week. At Week 12, there was a mean change from baseline of -11.8 (tolterodine ER), -6.9 (placebo), and -10.6 (tolterodine IR) with large standard deviations of 15.4 to 17.8 incontinence episodes per week. This resulted in a **treatment difference for tolterodine ER versus placebo of -4.8 incontinence episodes per week least square estimated mean change (SEM 1.0)**. It should be noted that the calculation of sample size was based on the primary efficacy variable, a standard deviation of 18.2, and "a minimal difference worth detecting" (Vol. 48/51 pg. 11) between tolterodine ER and placebo of four

incontinence episodes per week. The tolterodine ER compared to placebo results met the "minimal difference worth detecting" of four incontinence episodes per week. The 97.5% CI were (-7.2, -2.5) with a p-value of 0.0001. No subgroup analysis was done based on individual subject race since non-Caucasians races represented only approximately 5% of the population. However analyses were done for White and for the remaining races pooled together.

At Week 12 compared to baseline, there was a statistically significant change of -0.6 micturitions/24 hours with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of 20.1 ml in mean voided volume per micturition with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (-0.2) in the number of pads per 24 hours used with tolterodine ER treatment versus placebo.

Reviewer's comments:

1) Lack of decrease in number of pads with treatment may be a key issue for reimbursement calculations in some European countries.

Patient's perception of bladder condition, perception of urgency, and perception of treatment benefit data was simply listed as percentages in each category with no additional statistical analysis.

Of note regarding their **perception of bladder condition** at Week 12 compared to baseline:

- 42.9% of placebo subjects reported improvement
- 57.6% of tolterodine ER subjects reported improvement
- 44.3% of placebo subjects reported no change
- 43.9% of tolterodine ER subjects reported no change

Of note regarding their **perception of urgency** at Week 12 compared to baseline:

- 25.8% of placebo subjects reported improvement
- 38.9% of tolterodine ER subjects reported improvement
- 64.2% of placebo subjects reported no change
- 55.0% of tolterodine ER subjects reported no change

Of note regarding their **perception of treatment benefit** at Week 12 compared to baseline:

- 22.0% of placebo subjects reported much benefit
- 41.2% of tolterodine ER subjects reported much benefit
- 43.5% of placebo subjects reported no benefit
- 24.1% of tolterodine ER subjects reported no benefit

Secondary efficacy endpoints of proportion of micturitions associated with urgency and urine weight per incontinence episode were omitted due to sponsor's assessment of unreliable data.

Subgroup efficacy analyses were performed by gender, age (<65 years, ≥ 65 years), race (White, other) and metabolizer type (extensive, poor) for the ITT population.

Reviewer's comments:

- 1) Overall, there were no significant differences in efficacy by age.
- 2) There were no significant differences in efficacy by gender with the exception that the change in mean volume voided from baseline to week 12 was higher in females (37.9 ml/micturition with SD 50.8) than in males (16.4 ml/micturition with SD 45.2) on tolterodine ER. It should be noted that there was significant variability in the mean volume voided as reflected in the large standard deviations (SD).
- 3) There was an insufficient number of non-white patients (tolterodine ER n=24; placebo n=29) to draw any conclusions about racial efficacy differences.
- 4) There was an insufficient number of poor metabolizer patients (tolterodine ER n=29; placebo n=30) to draw any conclusions about metabolizer type efficacy differences.
- 5) Subgroup analysis was not performed by subgroups defined by baseline mean number of incontinence episodes per week. Majority of improvement may have occurred in subjects with large numbers of incontinence episodes.
- 6) Subgroup analysis was not performed by subgroups defined by baseline number of micturitions per 24 hours.

Quality of Life Data (Vol. 26/51 pg. 94-95 and Vol. 48/51 Appendix 23 pg. 3-121) were reviewed. The King's Health Questionnaire (KHQ) was considered the primary HRQOL measure and the SF-36 a secondary HRQOL measure. The KHQ is a disease-specific HRQOL instrument that was developed specifically for urinary incontinence patients. For the KHQ, 100 indicates the worst possible HRQOL and 0 indicates the best possible HRQOL. The developers of the KHQ have not published guidance on the difference in KHQ scores that is perceptible to the patient and clinically meaningful. The Sponsor determined meaningful differences by determining the patient's mean change in HRQOL score when the patients indicated a change in their disease with the global rating of disease severity. The protocol (Section 9.1) stated that all evaluations of the KHQ and the SF-36 were to be performed as specified in the respective manuals.

In the KHQ, ten separate scores are generated: one from each of seven domains, two from one-item questions addressing General Health Perceptions and Incontinence Impact, and a separate Symptom Severity scale score. Totalling the ten scores is not part of the KHQ. Two of the ten scores (**Role Limitations** domain and the **Severity (coping) Measures** domain) exceeded the "minimum criteria for meaningful difference" when tolterodine ER treatment was compared with placebo. The two scores just exceeded the minimal criteria to be considered a meaningful improvement by 0.61 to 1.09, which were very small margins considering the possible 100 mean change score).

The **Role Limitations** domain score for tolterodine ER treatment compared with placebo showed a difference in mean change score of -7.36. The minimal criterion to be considered a meaningful improvement in this domain was -6.75. The Role Limitation domain measured the limitations imposed on the patient's ability to perform household tasks, perform work, and carry out other normal daily activities.

The **Severity (coping) Measures** domain score for the tolterodine ER treatment compared with placebo showed a difference in mean change score of **-5.58**. The minimum criterion to be considered a meaningful improvement in this domain was **-4.49**. The **Severity (coping) Measures** domain was of secondary interest in this study and measured the patient's behaviors used to cope with their overactive bladder, such as wearing pads, monitoring fluid intake, and changing clothes, as well as worrying about an odor or experiencing embarrassment.

Regarding the **Incontinence Impact** question, tolterodine ER was 75.89 at baseline and 60.20 at end of treatment (-15.68 mean change) and placebo was 75.92 at baseline and 67.06 at end of treatment (-8.86 mean change) with a difference in mean change score of **-6.75**. The minimum criterion to be considered a **meaningful improvement** with this question was **-7.91**, which was **not met**, however it was statistically significant from placebo using the Hochberg procedure. The **Incontinence Impact** question for tolterodine IR met the minimum criterion to be considered a meaningful improvement.

The **Short Form-36** can be analyzed by eight domains or summarized as Physical Component Summary (PCS) and Mental Component Summary (MCS) measures. There were **no statistically significant differences** between treatment groups on the SF-36 PCS and MCS scores. For SF-36, 0 indicates the worst possible HRQOL and 100 indicates the best possible HRQOL. Regarding the SF-36 Physical Summary scores, tolterodine ER was 43.74 at baseline and 44.93 at end of treatment (0.97 change) and placebo was 43.35 at baseline and 44.08 (0.72 change). Regarding the SF-36 Mental Summary scores, tolterodine ER was 48.14 at baseline and 48.81 at end of treatment (0.67 change) and placebo was 49.25 at baseline and 49.36 (0.10 change).

In summary regarding the **primary efficacy endpoint ITT Population**, there was a mean decrease of 11.8 incontinence episodes per week (from baseline of 22.1) with tolterodine ER treatment versus a mean decrease of 6.9 incontinence episodes per week (from baseline of 23.3) with placebo. This difference of **4.8 less incontinence episodes per week** with tolterodine ER treatment compared with placebo was a statistically significant decrease and the sponsor concluded that it was also a clinically meaningful decrease. The sponsor utilized a difference of **4.2 less incontinence episodes per week** in determining the sample size (Vol. 26/51 pg. 73) and stated "a **minimal difference worth detecting of four incontinence episodes**" per week was used to calculate the sample size (Vol. 48/51 p. 11). If 4.2 less incontinence episodes per week were accepted as the minimal difference worth detecting, **the ITT tolterodine ER population met this criterion** when compared to placebo.

The sponsor omitted discussing if the subject considered a mean decrease of one incontinence episode approximately every two days to be of sufficient clinical benefit for them to accept the risks of treatment. During the End of Phase 2 meeting for NDA 21-228 on November 30, 1998, DRUDP advised sponsor to determine what change in incontinence episodes from baseline would be meaningful to the patient. DRUDP stated that a **clinically meaningful difference might be a 20-25% decrease in weekly incontinence episodes per week**. Placebo ITT subjects experienced a 30% decrease in weekly incontinence episodes per week. Tolterodine ER ITT subjects experienced a 53% decrease in weekly incontinence episodes per week. **Tolterodine ER ITT subjects demonstrated a 23% decrease in weekly incontinence episodes per week as the treatment difference when compared to placebo.**

Regarding the **secondary efficacy endpoints**, there were several statistically significant improvements demonstrated. It was unclear if they were clinically significant.

4.9.2.2 PP Population Efficacy Results

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.9-23.5 incontinence episodes per week. However, patients reported a very wide range of baseline incontinence episodes per week. The placebo and tolterodine ER patients reported 5 to 168 incontinence episodes per week at baseline. The tolterodine IR patients reported 5 to 141.2 incontinence episodes per week at baseline. At Week 12, there was a mean change from baseline of -13.5 (tolterodine ER), -8.8 (placebo), and -12.8 (tolterodine IR). This resulted in a treatment difference for **tolterodine ER versus placebo of -4.7 incontinence episodes per week** least square estimated mean change (SEM 1.3). The 97.5% CI were (-7.5, -1.8) with a p-value of 0.0002.

At Week 12 compared to baseline, there was a statistically significant change of **-0.5 micturitions/24 hours** with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of **23.3 ml** in mean voided volume per micturition with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (**-0.3**) in the **number of pads per 24 hours** used with tolterodine ER treatment versus placebo.

Of note regarding their **perception of bladder condition** at Week 12 compared to baseline:

- 47.6% of placebo subjects reported improvement
- 61.8% of tolterodine ER subjects reported improvement
- 39.8% of placebo subjects reported no change
- 31.4% of tolterodine ER subjects reported no change

Of note regarding their **perception of urgency** at Week 12 compared to baseline:

- 31.6% of placebo subjects reported improvement
- 43.5% of tolterodine ER subjects reported improvement
- 56.7% of placebo subjects reported no change
- 51.0% of tolterodine ER subjects reported no change

Of note regarding their **perception of treatment benefit** at Week 12 compared to baseline:

- 23.5 % of placebo subjects reported much benefit
- 43.2 % of tolterodine ER subjects reported much benefit
- 44.9 % of placebo subjects reported no benefit
- 22.1 % of tolterodine ER subjects reported no benefit

Subgroup analysis was not presented for the PP population by gender, age (<65 years, ≥ 65 years), race (White, other) and metabolizer type (extensive, poor). Quality of Life Data was not presented for the PP Population.

In summary regarding the **primary efficacy variable PP Population**, there was a mean decrease of 13.5 incontinence episodes per week (from baseline of 22.9) with tolterodine ER treatment versus a mean decrease of 8.8 incontinence episodes per week (from baseline of 23.5) with placebo. ~~This difference of 4.7 less incontinence episodes per week with tolterodine ER treatment compared with placebo was a statistically significant improvement. It is unclear whether this difference is clinically significant.~~

In summary regarding the **secondary efficacy variables PP Population**, there were several statistically significant improvements demonstrated. It was unclear if they were clinically significant.

4.9.2.3 Observed Cases Efficacy Results

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.5-22.7 incontinence episodes per week. However, the placebo and tolterodine ER arms had a very wide range from baseline 0 to 168 incontinence episodes per week and tolterodine IR also widely ranged from 0 to 141.2. At Week 12, there was a mean change-from baseline of -13.6 (tolterodine ER), -8.2 (placebo), and -12.3 (tolterodine IR). This resulted in a treatment difference for tolterodine ER versus placebo of **-5.3 incontinence episodes per week** least square estimated mean change (SEM 1.2). The 97.5% CI were (-8.0, -2.6) with a p-value of 0.0001.

At Week 12 compared to baseline, there was a statistically significant change of **-0.6 micturitions/24 hours** with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of **23.0 ml** in mean voided volume per micturition with tolterodine ER treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (**-0.3**) in the number of pads per 24 hours used with tolterodine ER treatment versus placebo.

Of note regarding their **perception of bladder condition** at Week 12 compared to baseline:

- 45.9% of placebo subjects reported improvement
- 60.5% of tolterodine ER subjects reported improvement
- 40.4% of placebo subjects reported no change
- 31.7% of tolterodine ER subjects reported no change

Of note regarding their **perception of urgency** at Week 12 compared to baseline:

- 27.9% of placebo subjects reported improvement
- 41.0% of tolterodine ER subjects reported improvement
- 61.3% of placebo subjects reported no change
- 52.6% of tolterodine ER subjects reported no change

The sponsor failed to submit the Observed Cases-population perception of treatment data. Subgroup analysis was not presented by gender, age (<65 years, ≥ 65 years), race (White, other) and metabolizer type (extensive, poor) for the Observed Cases-population. Quality of Life Data was not presented for the Observed Cases-Population.

In summary regarding the primary efficacy variable Observed Cases-population, there was a mean decrease of 13.6 incontinence episodes per week (from baseline of 22.7) with tolterodine ER treatment versus a mean decrease of 8.2 incontinence episodes per week (from baseline of 22.6) with placebo. This difference of 5.3 less incontinence episodes per week with tolterodine ER treatment compared with placebo was a statistically significant improvement. It is unclear whether it is clinically significant.

Regarding the secondary efficacy variables Observed Cases-population, there were several statistically significant improvements demonstrated. It is unclear whether they are clinically significant.

Reviewer's comment:

- 1) There were no significant differences between the Per Protocol-population and Observed Cases-population efficacy data.

4.10 Safety analyses

The analysis population for safety evaluation included all subjects who received at least one dose of study medication. Demographics, ECG and laboratory variables were analyzed descriptively, and adverse events were summarized. Three common adverse events (dry mouth, constipation, and headache) were analyzed in subgroups defined by gender, age, and metabolizer type. A total of 505 tolterodine ER subjects and 507 placebo subjects were evaluable for safety. Two tolterodine ER subjects and one placebo subject did not receive study medication and were excluded from the safety analysis.

4.10.1 Serious Adverse Events

In this study, serious adverse events (SAEs) were defined per FDA standard: death, life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect.

Two deaths occurred during the study; one subject was on tolterodine ER treatment and one subject was on placebo treatment. Patient 2404 (the tolterodine ER death) was a 54-year-old female who died on treatment day 32 as sudden death. The autopsy reported cause of death was ulcerated coronary atherosclerosis. Patient 1790 (the placebo death) was an 84-year-old female with intestinal ischemia due to vascular thrombosis after hospitalization for a fractured hip.

During treatment, 8 SAEs were reported in 7 tolterodine ER subjects and 18 SAEs were reported in 18 placebo subjects. A comparison of selected SAEs is presented in Table #2. The SAEs selected were known to be affected by muscarinic receptor antagonists, were gastrointestinal SAEs, or were cardiovascular SAEs. One tolterodine ER and 8 placebo subjects prematurely withdrew from treatment due to serious adverse events. Two tolterodine ER subjects (Patients 1108 and 1471) experienced SAEs that were considered by the investigator to be related to study treatment, however neither were prematurely withdrawn from treatment due to the SAE.

Table #2-Serious Adverse Events During Treatment by Treatment Group
(Created by MO from Table 23 Vol. 26/51 pg. 104)

	Tolterodine ER	Placebo
	Subject Number	Subject Number
Angina pectoris		2821
Chest Pain		1955
Ileus		2026
Intestinal obstruction	1108	1752
Nausea/Vomiting		1415
Palpitation	1471	
#SAEs Listed Above	2	5
Additional SAEs	8	13
Total # SAEs	10	18

After the end of study treatment, 3 SAEs were reported in 2 tolterodine ER subjects and 5 SAEs were reported in 4 placebo subjects. Table #3 lists the AE WHO preferred term for each of these subjects. In reviewing the subject narratives (Vol. 26/51 pg. 113-121), tolterodine ER Patients 2404 died on treatment day #32 and it is unclear why she was reported as an "after the end of study treatment" SAE. The subject narratives also stated that placebo Patients 1790 and 2339 experienced a SAE within 24 hours after termination of treatment and they were both prematurely withdrawn from the study due to their SAE. Regarding the "after the end of study treatment" SAEs, three patients recovered from their SAE, one patient recovered with sequel (Patient #2821), two subjects died (Patients # 1790 and 2404), and one patient (Patient # 2339 with schizophrenic reaction) had not recovered by the follow-up contact.

Table #3-Serious Adverse Events After the End of Treatment by Treatment Group
(Created by MO from Table 24 Vol. 26/51 pg. 105)

	Tolterodine ER Subject Number	Placebo Subject Number
Asthenia		1257
Cardiac Failure		2821
Chest pain	1830	
Myocardial infarction		2821
Intestinal ischemia		1790
Schizophrenic reaction		2339
Sudden death	2404	

Reviewer's comments:

- 1) The SAE tabulation and narratives were reviewed. No pattern of unexpected SAEs were identified in the Study-007 data reviewed. There were similar numbers and types of SAEs reported in the placebo and tolterodine ER arms.
- 2) It is the reviewer's opinion that the three subjects experiencing SAEs within 24 hours after the end of treatment should be included in the analysis of subjects experiencing

SAEs during treatment. Two patients died and one was prematurely withdrawn from the study due to the SAE.

4.10.2 Frequent Adverse Events

Adverse events that occurred with $\geq 5\%$ incidence by WHO body system are presented in Table #4.

Table #4-Incidence of Adverse Events $\geq 5\%$ by WHO Body System
(Created by MO from Table 19 Vol. 26/51 pg. 97)

	Tolterodine ER	Placebo
Autonomic nervous	24.2%	7.9%
Gastrointestinal	16.8%	14.2%
General	15.6%	15.2%
Respiratory	7.1%	4.9%
Urinary	7.1%	5.9%
Psychiatric	6.9%	5.1%
Vision	5.5%	2.8%
Central & peripheral nervous	5.0%	3.4%

Incidences (%) of adverse events exceeding placebo rate and reported in $\geq 1\%$ of patients treated with tolterodine ER and listed by WHO preferred term are presented in Table #5.

Table #5-Adverse Events Exceeding Placebo Rate and Reported in $\geq 1\%$ of Patients Treated with Tolterodine ER by WHO Preferred Term
(Created by MO from Table 20 Vol. 26/51 pg. 99)

	Tolterodine ER	Placebo
Mouth dry	23.4%	7.7%
Headache	6.3%	4.5%
Constipation	5.9%	4.3%
Abdominal pain	3.8%	1.6%
Xerophthalmia	3.4%	2.0%
Dyspepsia	3.0%	1.4%
Somnolence	2.8%	1.8%
Upper respiratory tract infection	2.8%	2.6%
Dizziness	2.2%	1.0%
Fatigue	2.2%	0.8%
Flatulence	2.0%	1.8%
Sinusitis	1.8%	0.6%
Edema peripheral	1.4%	0.8%
Hypertension	1.4%	1.2%
Vision abnormal	1.2%	0.4%
Pain	1.2%	1.0%
Dysuria	1.0%	0.2%