

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-771

MEDICAL REVIEW(S)

NDA 20-771

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Medical Officer Review

Sponsor: Pharmacia and Upjohn

Drug: **Generic:** Tolterodine

Trade: Detrusitol Tablets

Chemical: (R)-N, N- Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenyl
 propanamine L- hydrogen tartrate

Route: Oral

Dosage Form: Tablets BID

Strength: 1 mg and 2 mg

Proposed indication: Treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Related INDs:

1.0 Resume

Safety: The safety review of the submitted NDA was based on two data bases. The short term experience (up to 12 weeks) is presented on approximately 1600 patients who took tolterodine during phase 2 and 3 trials and long term experience included patients reported in the ISS submitted with the NDA and a 4-month safety update submitted on 7/24/97 which includes data through 4/30/97. The long term data base involved 1645 patients who took tolterodine for 6 months and 812 patients with 12 months of drug exposure.

The reviewer believes that there are three areas of concern regarding the safety of tolterodine. These are exaggerated antimuscarinic effects, cardiac abnormalities and adverse events related to disturbances or deficiencies of the cytochrome P450 system. The incidence of constipation, abnormal accommodation, constipation and urinary retention was quite low and in some cases exceeded background rates but this was not clearly demonstrated. The most common antimuscarinic adverse event was dry mouth. In the controlled studies, the incidence of dry mouth tended to be higher in the tolterodine groups than in placebo groups and highest in the oxybutynin groups. The incidence of

dry mouth in the long term studies was approximately 40%. Because of the subjective nature, lack of definition of the event and insufficient evidence as to what constituted a clinically meaningful difference, comparisons between tolterodine and oxybutynin are not appropriate for this parameter. In addition, the incidence of dry mouth with oxybutynin was similarly ill-defined.

Cardiac safety of tolterodine was extensively studied because of its structural similarity to terodiline. Terodiline is a drug that was intended for use in patients with detrusor overactivity because of its antimuscarinic activity. However, it also had calcium channel blocking and other effects that increased the QT interval in human beings which may have resulted in ventricular dysrhythmias including torsades de pointes. These problems were not found with tolterodine. Extensive cardiac studies in dogs indicated a wide margin of safety with respect to prolongation of QT interval (see pharmacology/toxicology report by Dr. Alex Jordan). Careful cardiac monitoring took place during all phases of development. Special subgroups such as the elderly and poor metabolizers were monitored in short term trials. In phase 3 (12 week) and long term studies (6-12 months), patients were monitored for QT interval, other EKG changes, arrhythmias, as well as clinical signs and symptoms of cardiac disease. There were no data from these studies that indicated that tolterodine precipitated cardiac events.

As described in section 2.2, tolterodine is metabolized by the cytochrome P450 system. Poor metabolizers were deficient in the 2D6 portion of the system. About 6% of the Caucasian population have this deficiency. In these cases, tolterodine was metabolized via the 3A4 enzyme route. In an analysis of adverse events by poor and extensive (normal) metabolizers within individual studies and by all studies, there appeared to be a higher incidence of dry mouth in the extensive metabolizers with more accommodation problems and urinary retention in the poor metabolizers. The reviewer did not consider this to be clinically significant because of the small numbers involved. The general adverse event profile was similar between the two groups. Problems might arise in individual patients who are poor metabolizers and are taking medications that block the 3A4 enzyme or patients who are extensive metabolizers taking medications that block 2D6 and 3A4. This area is further discussed in the Clinical Pharmacology and Biopharmaceutics review by Dr. Gary Barnette.

Clinical

The primary endpoint for the central efficacy studies submitted in this NDA (008,009,010) was the change in mean number of micturitions per 24 hours from baseline to end of study (12 weeks). Important secondary endpoints were changes in mean number of incontinence episodes per 24 hours and mean volume voided per micturition. As the analysis of the individual studies indicated, tolterodine was superior to placebo in two of the three central studies (008,009) with regard to changes in mean micturitions per 24 hours. In none of the individual studies (008,009,010) was tolterodine found to be superior to placebo for changes in mean number of incontinence episodes per 24 hours. Although in each study tolterodine was more efficacious than placebo for the incontinence parameter, this difference did not reach statistical significance. The change

in mean volume voided was considered by the reviewer to be an important physiologic indicator of the antimuscarinic effect of the tested drugs. Tolterodine was superior to placebo in all three studies (008,009,010) for this parameter.

The sponsor submitted an analysis of the pooled data for the three central studies (008,009,010). The reviewer believes that the "pooled" analysis can be supportive as the protocols of the three "pooled" studies were very similar. In the pooled analysis, tolterodine both 1 and 2 mg are superior to placebo for the change in mean episodes of incontinence per 24 hours. The reviewer believes that when the data from both the individual and "pooled" studies are considered, superiority of tolterodine 1 and 2 mg to placebo with regard to change in mean number of incontinent episodes per 24 hours is demonstrated. The "pooled" data also confirmed superiority of tolterodine 1 and 2 mg to placebo for the micturition and voided volume parameters. It should be noted that in phase 3 clinical studies no efficacy or safety differences between tolterodine 1 and 2 mg were demonstrated. On 12/5/97, the sponsor submitted, individual and pooled analysis of the three central studies (008,009,010) using changes in the median values for each endpoint rather than the mean values. The reviewer believes that this approach may have some validity especially for the incontinence data which tends to have a nonparametric distribution. The median analysis supported the conclusions noted above regarding the efficacy of tolterodine 1 and 2 mg for the micturition, incontinence and voided volume parameters.

In two of the central studies (008,010), oxybutynin 5 mg tid was used as an active comparator. In these individual studies as well as the two "pooled" analyses, oxybutynin tended to demonstrate increased efficacy compared to tolterodine. For this reason, the reviewer believes that the decreased "dry mouth" observed in patients taking tolterodine compared to oxybutynin during these trials was a result of reduced antimuscarinic effect of tolterodine and does not represent a superior therapeutic ratio.

In conclusion, tolterodine (1 and 2 mg po bid) is safe and effective therapy for the treatment of bladder overactivity with symptoms of urinary frequency, urgency or urge incontinence.

2.0 Background

2.1 Regulatory History: On 9/2/94, IND [redacted] was submitted to The Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160). On 4/24/95, the sponsor held a meeting with HFD-160 to discuss the results of their phase 2 trials (end-of-phase 2 meeting) and proposed plans for phase 3 trials. Another end-of-phase 2 meeting was held with the sponsor and The Division of Metabolic and Endocrine Drug Products (HFD-510) on 2/20/96 as tolterodine had been transferred to this division. The pre-NDA meeting was held with The Division of Reproductive and Urologic Drug products (HFD-580) on 9/24/96 as a result of formation of this new division from HFD-510. On 3/24/97, The NDA for tolterodine was submitted to HFD-580.

2.2 Clinical Background and Scientific Rationale

Clinical Background: Urinary incontinence, which is the involuntary loss of urine, is estimated to effect in some form 10- 35% of the adult US population and half of nursing home residents. The incidence increases with age and urinary incontinence is one of the major cause of institutionalization of the elderly. A recent estimate of the direct cost of caring for all incontinent patients in the community is \$11.2 billion and \$5.2 billion in nursing homes.¹

The two most common types of incontinence are stress and urge incontinence. They can often coexist and this is called mixed incontinence. Stress incontinence is manifested by loss of urine during an activity that increase intra-abdominal pressure such as coughing or sneezing. This type of incontinence is caused by one of two abnormalities of the urinary sphincter. The most common type is urethral hypermobility which is a weakness in the pelvic floor musculature. The second type in caused by an intrinsic malfunction of the sphincter itself.

Urge incontinence is the involuntary loss of urine associated with a strong desire to void. This type of incontinence is attributed to an involuntary contraction of the detrusor muscle, although this often cannot be demonstrated on a cystometrogram. According to the recommendations of the Urodynamic Society,² the generic term for an involuntary detrusor contraction is **Detrusor Overactivity**. This is the term that is used when the etiology of the involuntary contraction is unclear. When the contraction is caused by neurologic pathology, the condition is called **Detrusor Hyperreflexia**. In the absence of a neurologic lesion the condition is called **Detrusor Instability**.

Physiology and Metabolism:

Detrusor muscle contractions are mainly mediated through cholinergic muscarinic receptor stimulation. Inappropriate detrusor contraction can lead to a sensation of urgency (an exaggerated sense of the need to micturate). Increased urgency can lead to urinary frequency, nocturia and "urge incontinence," if the urge to void cannot be resisted. The main pharmacologic therapy for this problem is directed at reducing the activity of the detrusor muscle with antimuscarinic drugs. The therapy must generally be given long-term as drug therapy only controls the condition and does not offer cure.

¹ Urinary Incontinence in Adults: Acute and Chronic Management, Agency for Health Care Policy and Research, 1992 Update.

² Blaivas, Appell et al, Definition and Classification of Urinary Incontinence: Recommendation of the Urodynamic Society, *Neurourology and Urodynamics* 16:149-151 (1997)

Oxybutynin is currently the most commonly used therapy, pharmacologic or otherwise, for urgency incontinence. Over 70% of urologists recently stated that oxybutynin was their first treatment option in the management of this condition.³ The sponsor believes that although oxybutynin has a favorable efficacy profile, it does not have selectivity for bladder smooth muscle over tissues such as salivary glands. Thus the usefulness of oxybutynin is limited by the severity of adverse events, mainly dry mouth. The Division recognizes that many patients discontinue the use of this medication and similar drugs because of dry mouth and related anti-cholinergic adverse events such as reduced visual accommodation and constipation. The sponsor believes that tolterodine is a competitive muscarinic antagonist that exhibited selective antimuscarinic activity for bladder compared to salivary gland. Therefore, tolterodine was expected to be at least as effective as oxybutynin with reduced adverse events especially dry moth. The sponsor hoped that this would result in improved tolerability and compliance.

Tolterodine is primarily metabolized to the 5-hydroxymetabolite (DD 01), an active metabolite, by the isoenzyme CYP2D6 (see figure 1). Subjects that are deficient in CYP2D6 (about 7% of the caucasian population) are considered poor metabolizers. In these individuals, higher concentrations of tolterodine are exhibited with non-measurable DD 01. Extensive metabolizers are not deficient in CYP2D6. In poor metabolizers an alternative metabolic pathway involving CYP3A is active (the resultant metabolite does not contribute to the clinical effect). DD 01 exhibits antimuscarinic activity similar to tolterodine. This metabolite is believed to contribute significantly to the therapeutic effect in extensive metabolizers. Metabolism is further discussed in the Pharmacology review by Dr. Gary Barnette. No gender dependent differences in the pharmacokinetic profile of tolterodine or DD 01 were observed.

³ Survey conducted at the 1997 annual meeting of the American Urologic Association of a total of 155 US and 264 non-US urologists.

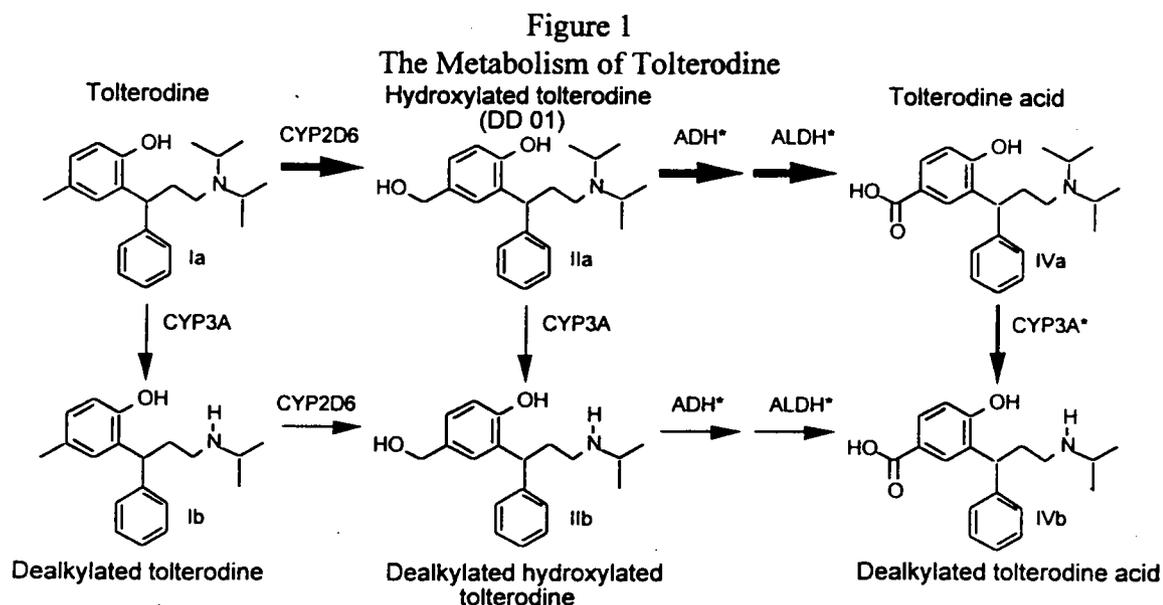


Figure 6.4 Identified urinary metabolites in human beings and proposed metabolic pathways.
*Indicates tentative enzyme.

Tolterodine is hydroxylated to a pharmacologically active metabolite DD 01, which subsequently is oxidised to the corresponding acid which is dealkylated. The metabolites shown in Figure 6.3 have been identified in urine after [¹⁴C]-tolterodine administration (90-126-00, Norén et al., 1991 and Edlund et al., 1993).

Reviewer's Comment: A potential safety problem could arise in a poor metabolizer who is on a drug that interferes with CYP3A activity (e.g., Ketoconazole, erythromycin). This issue is examined closely in the Clinical Pharmacology Review.

Dose Selection: During phase 1 and 2 studies, it was determined that a dose of 0.5 mg bid was the no-effect dose and a dose of 4 mg bid dose was the maximally tolerated dose. The intermediate doses of 1 and 2 mg bid were chosen for the phase 3 trials. At these dosage levels and schedule the sponsor believes that accumulation of tolterodine and DD 01 would be low since the half life of tolterodine is 2-3 hours and 3-4 hours for DD 01. In poor metabolizers, accumulation would also be low.

During efficacy evaluation in 4 phase 2 trials, it was demonstrated that tolterodine 1 and 2 mg bid resulted in "clinically relevant" improvements in the symptoms of urge incontinence without significant increases in residual post-void bladder volume. The 4 mg bid dosing regime, however, resulted in an increase in post void residual volume. Despite a relatively short half-life, the twice daily regimen was shown to be adequate for a sustained pharmacodynamic effect.

2.3 International marketing experience

Approval of tolterodine was accomplished during the last several months in Sweden. The sponsor will seek European approval on this basis. No data from use in Sweden is available to the reviewer.

3.0 Summary of NDA clinical section

The clinical section of this application contains the study reports of the three controlled "core" studies and a supportive study; all reviewed below. These studies were 12 week studies. In addition, the submission includes four randomized controlled 4 week studies. Phase 2 and safety follow-up studies are also included.

3.1 Summary of submitted controlled trials of tolterodine--"Core studies"

CTN 94-OATA-008 (Part A)

This was a multicenter, randomized, double-blind, double-dummy, controlled trial comparing tolterodine 2mg. b.i.d. with oxybutynin 5 mg. t.i.d. and placebo in patients with detrusor instability. Two hundred and ninety-three patients were randomized to treatment at 42 centers (23 in the United Kingdom, 4 in Ireland and 15 in Sweden). The first patient was recruited on July 14, 1995, and the last patient completed the study on July 15, 1996. Patients were randomized after a two week wash-out period to a twelve week study. Those who completed the 12 week study were invited to participate in an open label long term follow up study which was to last 9 months (CTN 94-OATA-008 [Part B]). The **primary efficacy variable** was the change in mean number of micturitions per 24 hours. The important **secondary efficacy variables** were the changes in mean number of incontinence episodes per 24 hours and the mean volume voided per micturition.

CTN 94-OATA-009 (Part A)

This was a multicenter, multinational, randomized, double-blind, placebo controlled trial comparing tolterodine 1mg. b.i.d., tolterodine 2mg. and placebo in patients with detrusor overactivity. Three hundred sixteen patients were randomized to treatment at 25 centers (18 in the USA and 7 in Australia). The first patient was recruited on 11 September 1995 and last patient completed assessments on Oct. 8, 1996. Patients were randomized after a two week wash-out period to a twelve week study. Those who complete the 12 week study are invited to participate in an open label long term follow up study involving treatment with tolterodine 2mg. bid for 9 months (CTN 94 OATA-009 Part B). The **primary efficacy variable** was the change in mean number of micturitions per 24 hours. The important **secondary efficacy variables** were the changes in mean number of incontinence episodes per 24 hours and the mean volume voided per micturition.

CTN 94-OATA-010 (Part A)

This was a multicenter, randomized, double-blind, double-dummy, controlled trial comparing tolterodine 2mg. b.i.d. with oxybutynin 5 mg. t.i.d. and placebo in patients with detrusor overactivity. Two hundred and seventy-seven patients were randomized to treatment at 25 centers (15 in the United States, 10 in Canada). The first patient was recruited on October 2, 1995, and the last patient completed the study on June 13, 1996.

Patients were randomized after a two week wash-out period to a twelve week study. Those who completed the 12 week study were invited to participate in an open label long term follow up study which lasted 9 months (CTN 94-OATA-010 [Part B]). The **primary efficacy variable** was the change in mean number of micturitions per 24 hours. The **secondary efficacy variables** were the changes mean number of incontinence episodes per 24 hours and the mean volume voided per micturition.

3.2 Summary of other clinical trials of tolterodine

The four-week, controlled, phase 2 studies and safety extensions presented in the submission do not add data that altered conclusions that were reached after reviewing the four submitted 12 week studies. Two brief (2 week) controlled studies (92-OATA-003, 93-OATA-005) were specifically designed for patients with detrusor hyperreflexia. These studies involved a total of about 175 patients with neurologic disease failed to demonstrate any statistically significant drug effect in the clinical endpoints.

4.0 Clinical trial CTN 94-OATA-008 (Part A)

4.1 Design and conduct of trial: This was a multicenter, randomized, double-blind, double-dummy, controlled trial comparing tolterodine 2mg. b.i.d. with oxybutynin 5 mg. t.i.d. and placebo. Two hundred and ninety-three patients were randomized to treatment at 42 centers (23 in the United Kingdom, 4 in Ireland and 15 in Sweden). The first patient was recruited on July 14, 1995, and the last patient completed the study on July 15, 1996. Patients were randomized after a two week wash-out period to a twelve week study. Those who complete the 12 week study were invited to participate in an open label long term follow up study which was to last 9 months (CTN 94-OATA-008 [Part B]).

Male and female patients over 18 years of age with detrusor instability were included in the study. Detrusor instability was demonstrated urodynamically by a detrusor contraction of equal to or more than 10 cm. of water during cystometry. No drugs effecting bladder function were permitted within 7 days of urodynamic investigation. During the run-in period, patients were required to have symptoms of urinary frequency defined as at least 8 micturitions on average per 24 hours. In addition patients were required to have symptoms of urge incontinence (at least one episode of incontinence on average per 24 hours) during the run-in period or urinary urgency or both. Patients were excluded if they had significant stress incontinence or neurological disease or injury that could affect the lower urinary tract or its nerve supply. Patients were additionally excluded if they had residual volumes of more than 200 ml, had a history of interstitial cystitis or had a total voided volume of more than 3000 ml on average per 24 hours.

Reviewer's comment:

- 1. Tolterodine was not tested in patients with detrusor hyperreflexia and therefore this trial does not support a claim for patients with neurologic disease.**

Following completion of a washout/run-in period (one week for naïve patients and two weeks for patients who had been on anti-incontinence medication), patients were randomized at visit 2 (day 1) to one of the following:

1. One tolterodine 2 mg tablet bid (morning and evening) and one placebo tolterodine tablet once daily (midday). These patients also took one placebo oxybutynin tablet tid.
2. One oxybutynin 5 mg tablet tid and one placebo tolterodine tablet tid.
3. One placebo tolterodine tablet tid and one placebo oxybutynin tablet tid.

The study period lasted 12 weeks. Patients were seen and evaluated at week 2 (visit 3), week 4 (visit 4), week 8 (visit 5) and week 12 (visit 6). There was a follow-up visit at least 2 weeks after visit 6 for assessment of adverse events. At the termination of the controlled study the patients were given the option to enter an open label safety study (94-OATA-008 part B).

There were two circumstances in which dose reduction could occur. In the first situation, in order to comply with the labeling of oxybutynin in the UK, investigators were given the option of starting patients over 65 years of age on a reduced dose of study medication (tolterodine 1 mg bid or oxybutynin 2.5 mg tid). After one week the dosage was increased to the normal study dose (tolterodine 2 mg bid or oxybutynin 5mg tid). If these patients did not tolerate the "normal" dose then the dose could be reduced as an alternative to withdrawal and only during the second week of the study. In the second situation, in the case of study medication intolerance, a patient could be placed on a reduced dose only as an alternative to withdrawal and only within 14 days of randomization. In both cases the following dose reduction was permitted:

1. One tolterodine 1 mg tablet bid (morning and evening) plus one placebo tolterodine tablet once daily (midday). One placebo oxybutynin tablet tid.
2. One oxybutynin 2.5 mg tablet tid and one placebo tolterodine tablet tid.
3. One placebo tolterodine tablet tid and one placebo oxybutynin tablet tid.

A computer generated randomization list was prepared by the sponsor using the method of random permuted blocks within centers. The block size was five. Patients who completed the wash-out/ run-in period and were eligible for the study were randomized to treatment with tolterodine, oxybutynin or placebo in the ratio 2:2:1 in accordance with the randomization list. The patient numbers had five digits. The first three digits identified the center and the last two digits identified patients randomized consecutively at the center. Informed consent was obtained before randomization. The codes could only be broken for medical necessity and in this case the situation had to be reported to the sponsor within 24 hours. A double-dummy design was used to maintain blinding. All patients took the same number of tablets in the morning, midday and evening. Tolterodine placebo tablets were indistinguishable from tolterodine tablets and

oxybutynin placebo tablets were indistinguishable from oxybutynin. There were two types of medication packages labeled "study dose" or "reduced dose."

The **primary efficacy variable** was the mean number of micturitions per 24 hours. A micturition chart printed in intervals of one hour was used to collect efficacy data. During the 7 day period preceding visit 2, 3, 4, 5, and 6 patients recorded the time of each spontaneous micturition, each incontinent episode and the number of pads used per 24 hours. The volume voided at each micturition was noted during 2 of the 7 day recording period. The **secondary efficacy variables** were the mean number of incontinence episodes per 24 hours, the mean volume voided per micturition, and the number of pads used per 24 hours. Only complete data for full 24 hour days were included in the calculation of the micturition parameters. Data obtained during any period of a confirmed urinary tract infection were excluded from the data.

Other efficacy parameters measured were a global assessment of the patient's perception of bladder function, a psychological well-being index, and a quality of life questionnaire.

Clinical safety assessments included ECG (measured at baseline and during part B of the study), BP within 6 hours of drug intake at visit 2,4 and 6 and residual urine measured at baseline and if the patient experienced symptoms of retention during the study.

Reviewer's comment:

1. **Residual urine should have been measured at some point during the study period.**

Adverse events were monitored in the routine fashion.

Laboratory safety assessments for routine blood laboratory tests were obtained at visit 1, 4, and 6 or at withdrawal. Samples were analyzed at a central laboratory. A midstream specimen of urine was obtained at visit 1.

Reviewer's comment: **A urine specimen should have been obtained during the study period to determine if asymptomatic urinary tract infection is more common in the drug groups.**

Drug serum concentrations of tolterodine and DD 01 (major active metabolite) along with oxybutynin and its desethylated metabolite were obtained at visit 1, 4, 6 or withdrawal within 6 hours of ingestion of the study drug. Analysis was done at a central laboratory.

4.2 Study Population: The intent-to-treat (ITT) population included all patients randomized to the study. The per-protocol population (PP) included all randomized patients who had completed the study without violating any major eligibility or protocol criteria. Patients who were withdrawn from treatment or who had dose reductions were excluded from the PP population. The safety population included those patients that were

randomized and received at least one dose of study medication (the same as the ITT population). Table 1 illustrates the relationship between the ITT and PP populations.

Table 1
Number of Patients in Intent-to-Treat (ITT) and Per-Protocol (PP) Population
(Study CTN 94-OATA-008)^a

	Tolterodine	Oxybutynin	Placebo	Total
ITT (N)	118	118	57	293
PP n, (n/N)	78, (68%)	45, (38%)	40, (70%)	163, (56%)

a-The Safety and the ITT population are the same in this study

A total of 293 patients were randomized to treatment. Fifty-seven received placebo, 118 tolterodine and 118 oxybutynin. In the ITT population there were no statistically significant differences with respect to baseline demographic characteristics.

Approximately 75% of each group were female. All patients except for one in each group were Caucasian. The mean age was approximately 56 years while the mean body mass index was about 27 kg/m².

Baseline parameters related to disease characteristics were similar among the three groups. Over 50% of patients had symptoms of urgency for over 5 years. Approximately 40% of the patients had previously taken drugs for urge incontinence and 30% had had surgery affecting the lower urinary tract. Micturition chart variables and urodynamic variables were similar among the three groups.

Approximately 80% of all groups had concurrent disease with hypertension (11%), postmenopausal disorders (8%) and asthma (4%) being the most common. Because of this, most of the patients in each group (85%) were taking concomitant medication during the study. These medications represented a wide variety of drug groups.

4.3 Withdrawals and compliance: A total of 47 patients were withdrawn from the study. There were 7/57 placebo patients (12%), 14/118 in the tolterodine group (12%) and 26/118 on the oxybutynin group (22%). The proportion of treatment withdrawals was significantly higher in the oxybutynin group than the tolterodine group.

Reasons for withdrawal were adverse events in all cases in the placebo group and in the majority of cases for the active arms of the study. Only one patient in each active arm was lost to follow-up while no patient was lost to follow-up in the placebo arm. Thirty-seven out of 47 patients that withdrew did so because of adverse events (79%). Dry mouth was the most common type of adverse event (18/37 or 49%). Dry mouth was the

cause for withdrawal in 2/7(29%) of the placebo group, 1/14(7%) of the tolterodine group and 15/26 (58%) of the oxybutynin group.

In Ireland and Sweden compliance was calculated on the basis of the number of returned tablets relative to the number of delivered tablets. In order for the patient to qualify for the PP analysis at least 86% of the doses had to be consumed. In the UK, patients were asked about compliance and if they were found to miss less than 3 doses per week, they were eligible for the PP analysis. Calculated compliance was over 90% for each dose group.

4.4 Protocol violations and deviations: A total of 82/293 patients (28%) had at least one major protocol violation. Twelve out of 57 in the placebo group (21%), 26/118 (22%) in the tolterodine group and 44/118 (37%) in the oxybutynin group had these violations. Patients who had violations were included in the ITT but excluded from the PP analysis. No valid micturition chart at entry and at week 12 accounted for 62/82 (75%) of the violations. This violation occurred in 9/51(16%) of the placebo, 18/118 (15%) of the tolterodine and 33/118 (25%) of the oxybutynin group.

There were several deviations from the original protocol and most were minor. The most significant deviation was the administration of a reduced dose of study medication in some patients over 65 years of age. Nine out of 293 patients in the study were in this category. There were 3/57 (5%) in the placebo group, 2/118 (2%) in the tolterodine group and 4/118 (3%) in the oxybutynin group. It was mandatory as part of the study for these patients to be increased to full dose on Day 8 and then only in the case of intolerance and as an alternative to withdrawal dose reduction was permitted the following week.

Reviewer's comment: Because of the small number of patients involved in "dose reduction" and the relatively even distribution, it is doubtful these reductions had a significant outcome on the results of the study.

4.5 Efficacy analysis

4.5.1 Statistical Methods: Differences between means and changes from baseline to endpoint are compared to show differences with a level of $P \leq 0.05$ considered to be significant.

When equivalence is determined, 95% confidence intervals are employed. Confidence intervals of ± 1.5 are used for both the micturition and incontinence variables.

Analysis of ITT population was the primary analysis. The ITT analysis was performed using the last observed data (the endpoint). However if data was missing at endpoint for any reason the principle of last observation carried forward was accomplished. If initial data was missing for any reason then data was brought backwards from the next visit. The PP analysis was performed as a supportive efficacy analysis.

Reviewer's comment:

1. It is unclear why the number "1.5" is chosen to define equivalence for both micturitions per 24 hours and incontinence per 24 hours. This number may be appropriate for the analysis of micturitions per 24 hours because baseline micturitions per 24 hours is approximately 11 and endpoints are approximately 9 so that 1.5 represents a variation of about $\pm 15\%$. However, baseline incontinence per 24 hours is approximately 3 while endpoint is about 1. This allows for variations of $\pm 50\%$. This amount of variation is too wide to reasonably conclude equivalence.

4.52 Efficacy Results: The primary analysis of the study was the comparison of the effect of treatment with tolterodine relative to oxybutynin and placebo on the micturitions per 24 hours. See table 2, 3 and 4.

Table 2
Mean Number of Micturitions per 24 Hours at Baseline and Endpoint (week 12)
Study- CTN 94-OATA-008 (ITT)

	Placebo	Tolterodine	Oxybutynin
Baseline	11.7	11.5	10.7
Endpoint	10.2	8.8	8.4
Change	-1.6	-2.7	-2.3
P	0.0019	0.0001	0.0001

Table 3
Change from Baseline to Endpoint (week 12) in Mean Number in Micturitions per 24
Hours, Comparative Analysis
Study- CTN 94-OATA-008 (ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-1.2	-0.7	-0.5
95% CI	-1.9 -0.4	-1.5, 0.1	-1.1, 0.1
P	.0022	.068	-----

Table 4
Change from Baseline to Endpoint (week 12) in Mean Number of Micturitions per 24 Hours
Study- CTN 94-OATA-008 (PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-1.3	-1.4	-0.5
95% CI	-2.2, -0.5	-2.4, -0.4	-1.1, 0.1
P	0.0028	0.0049	-----

Reviewer's comments:

1. **The data indicate that in the ITT population, tolterodine is statistically better than placebo in reducing micturitions per 24 hours during the treatment period. It is equivalent to oxybutynin using 95% CI. Oxybutynin is not statistically better than placebo in reducing micturitions per 24 hours in the ITT population but is in the PP population. Because of a high dropout rate secondary to adverse events (especially "dry mouth"), oxybutynin may not have been used long enough to demonstrate an effect.**

2. **The results of the PP population (table 4) are similar to the ITT except that oxybutynin is significantly better than placebo. This disparity may be caused by the situation that more patients taking oxybutynin were excluded from the ITT population to form the PP population than the tolterodine or placebo patients. The PP population only has patients who had been on study drug for the full 12 weeks. Therefore, there is a higher chance of oxybutynin achieving efficacy. Exclusions to form the PP population resulted in 70% and 66% of the placebo and tolterodine patients being available for analysis. However exclusions in the oxybutynin group allowed only 38% of patients to be available for PP analysis. Both the ITT and PP analysis yielded useful data regarding the efficacy of tolterodine.**

Important secondary parameters were mean incontinence episodes per 24 hours and mean volume voided per micturition. Tables 5,6,7,8,9, and 10 display these results.

Table 5
Mean Number of Incontinence Episodes per 24 Hours at Baseline and Endpoint (12 weeks)

Study- CTN 94-OATA-008 (ITT)

	Placebo	Tolterodine	Oxybutynin
Baseline	3.3	2.9	2.6
Endpoint	2.4	1.6	0.9
Change	-0.9	-1.3	-1.7
P	0.0009	0.0001	0.0001

Table 6
Change from Baseline to Endpoint (week 12) in Mean Number of Incontinence Episodes per24 Hours

Study- CTN 94-OATA-008 (ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-0.5	-0.9	0.4
95% CI	-1.2, 0.3	-1.6, -0.1	-0.2, 1.0
P	0.22	0.023	-----

Table 7
Change from Baseline to Endpoint (week 12) in Mean Number of Incontinence Episodes per24 Hours

Study- CTN 94-OATA-008 (PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-0.3	-0.80	0.4
95% CI	-1.1, 0.5	-1.7, 0.0	-1.2, 1.0
P	0.45	0.059	-----

Urinary incontinence was not an entry requirement for the study. The patients could have either urgency or urge incontinence. Because of this, a total of 67 patients were excluded from this analysis because they did not have incontinence at baseline. Twenty-six percent of the placebo group, 20% of the tolterodine group and 24% of the oxybutynin group were excluded. The PP group was then constructed in the same manner as previously mentioned.

Reviewer's comments:

1. **In the ITT and PP populations, tolterodine was not superior to placebo in improving incontinence episodes. However, oxybutynin is superior to placebo in the ITT population and is "almost" superior to placebo in the PP population (p=.059). It is of some concern that tolterodine is not superior to placebo in this parameter especially since the active control demonstrates superiority. However, the sponsor stated that the study was not powered to detect differences in incontinence.**

2. **The sponsor stated that tolterodine and the active control are "equivalent." However, since baseline incontinence per 24 hours is approximately 3, the confidence interval of ± 1.5 is too wide because it represents a variation of about $\pm 50\%$.**

An important secondary endpoint for this drug is change in volume per micturition. This is a reflection of the physiologic effect of the drug on the detrusor tone. See tables 8,9, and 10.

Table 8
Mean Volume voided per Micturition(ml) at Baseline and Endpoint (12 weeks)
Study- CTN 94-OATA-008 (ITT)

	Placebo	Tolterodine	Oxybutynin
Baseline	157	166	176
Endpoint	163	204	222
Change	6	38	47
P	0.30	0.0001	0.0001

Table 9
Change from Baseline to Endpoint (week 12) in Mean Volume Voided (ml) per
Micturition
Study- CTN 94-OATA-008 (ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	32	41	-9
95% CI	18, 46	26, 55	-20, 3
P	.0001	.0001	.15

Table 10
Change from Baseline to Endpoint (week 12) in Mean Volume Voided (ml) per
Micturition
Study- CTN 94-OATA-008 (PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	30	50	-9
95% CI	12, 47	30, 69	-20, 3
P	0.0011	0.0001	0.14

Reviewer's comments:

- Mean volume voided is an objective physiologic parameter. Both tolterodine and the active control were superior to placebo with increased bladder volume. It appeared, however, that the active drug response was greater than tolterodine. Although this difference was not statistically significant.**

Other secondary parameters included patient's perception of bladder condition, psychological well-being and quality of life.

Reviewer's comment: There were no significant trends in these parameters that could support efficacy claims.

4.6 Safety analysis

Deaths: There are no deaths related to study medication.

Serious or severe adverse events: Serious adverse events were reported for nine patients, two in the placebo group (4%), four in the tolterodine group (3%), and three in the oxybutynin group (3%). Of the four patients that had adverse events in the tolterodine group, three were clearly unlikely related to drug (rectal prolapse, ovarian carcinoma, arterial embolus after investigative procedure).

Some of the adverse events experienced by the other patient could have contributed to by tolterodine in the view of The Division. However, the death of the patient was unlikely due to tolterodine. Patient was an 80 year old man who experienced several episodes of syncope after about 2.5 months of treatment with tolterodine. The patient had preexisting cardiovascular disease and was on multiple medications. He experienced episodes of syncope both before and after he was on the study. EKG data around the time of these episodes indicated no evidence of arrhythmia of QT interval change. The patient was demonstrated to be orthostatic during these episodes. The patient's study medication was stopped after he completed the study on 1/24/96 having been on tolterodine since 11/2/95. On 4/8/96 the patient died after a few days of chest pain and vertigo. The reviewer does not believe that tolterodine contributed to this death.

All adverse events: The most frequently reported adverse events (AE) were autonomic nervous system disorders (dry mouth, abnormal accommodation and xerophthalmia). These occurred in 25% of the placebo group, 53% in the tolterodine group and 88% of the oxybutynin group. The second most common type of AE was gastrointestinal (constipation and "dyspepsia"). These occurred in 28% of the placebo, 33% of the tolterodine and 47% of the oxybutynin groups. Cardiovascular events were 2% in placebo and tolterodine and 1% in oxybutynin.

Dry mouth is by far the most commonly reported AE. Its incidence in each group is illustrated in Table 11.

Table 11
Proportion of Each Treatment Group that Reported Dry Mouth at Least Once in Study
CTN 94-OATA-008 (Part A)^a

	Placebo	Tolterodine	Oxybutynin
Percent	21	50	86

a. Tolterodine vs. placebo, oxybutynin vs. placebo and oxybutynin vs. placebo all $p < 0.001$

In addition to the fact that oxybutynin had an increased incidence of dry mouth compared to tolterodine, the patients reported the events as being more severe. During the study, 3 (5%) patients in the placebo group, 9 (8%) in the tolterodine group and 48 (41%) in the oxybutynin group reported "severe" dry mouth. As mentioned in section 4.3, the most common reason for withdrawal from the study was dry mouth. Overall 18 patients

withdrew because of dry mouth, 2 (4%) in the placebo, one(1%) in the tolterodine and 15 (13%) in the oxybutynin groups.

The proportion of patients withdrawn for any AE was higher in the oxybutynin than in the tolterodine group (17% vs. 8%, $p=0.051$) and the proportion of patients that required dose reduction was also higher in the oxybutynin vs. tolterodine groups (32% vs. 8%, $p<0.001$).

Laboratory and clinical safety parameters:

There were no clinically significant changes in **diastolic blood pressure** from baseline to week 12 in any group. There was statistically significant decrease in **systolic blood pressure** between tolterodine and oxybutynin group (- 6mmHg vs.-1mmHg, $p=.023$).

Reviewer's comment: These changes will be reviewed for the population of patients exposed to drug in all 12 week studies to see if these changes are significant.

There were some statistically significant changes in **chemistry and hematology** parameters from baseline to week 12 but there did not appear to be any clinically significant trends.

Reviewer's comment: A larger safety base will be evaluated and discussed later in this review to see whether these trends persist.

EKG was performed at baseline but not repeated during Part A of the study.

Reviewer's comment: Data from follow-up ECG's will be examined for safety problems and discussed later in the review.

Blood samples were drawn for determination of serum tolterodine and DD01 within 6 hours of drug intake at week 4 and 12. This was done for all patients but the analysis was done only for patients randomized to tolterodine. Tolterodine is metabolized by the cytochrome P450 enzyme CYP2D6, known to be absent in 7% of Caucasians. A patient was considered a poor metabolizer (PM) if the concentration of tolterodine was ≥ 1.0 ng/ml and the serum concentration of DD01 was ≤ 0.30 ng/ml. Other patients were considered to be extensive metabolizers (EM). This classification did not take into account possible concomitant drug intake. Classification was done on 109(92%) of the tolterodine patients and 7(6%) of those were found to be PM.

4.7 Reviewers assessment of safety and efficacy: The sponsor concluded that tolterodine was safe and better tolerated than oxybutynin. There were significantly fewer withdrawals and dose reductions in the tolterodine compared to the oxybutynin group and the overall intensity and frequency of dry mouth was less with tolterodine compared to oxybutynin. The sponsor argues that tolterodine significantly reduces micturition frequency compared to placebo and is equivalent in effect compared to oxybutynin. In addition, tolterodine reduces voided volume significantly compared to placebo. Therefore tolterodine was as effective in the treatment of detrusor instability as oxybutynin and is better tolerated.

The Division believes that tolterodine is superior to placebo in inhibiting micturitions and increasing volume per micturition. In this individual study, tolterodine is not superior to placebo in preventing incontinent episodes. The reviewer believes that oxybutynin may have an increased antimuscarinic effect over tolterodine which is expressed in both increased efficacy and increased incidence of antimuscarinic adverse events (i.e., dry mouth). The reviewer does not believe that oxybutynin and tolterodine are equivalent. The reviewer believes that tolterodine appears generally safe as expressed by the data in this study. Complete evaluation of the efficacy and safety of tolterodine requires examination of all studies and analyses (see section 8.0).

There are deficiencies in the study which are discussed in detail in the review. Major deficiencies are reviewed below:

Efficacy deficiencies:

- 1. Tolterodine was not tested in patients with detrusor hyperreflexia and therefore a claim cannot be made for patients with neurologic disease and urge incontinence.**
- 2. It is unclear why the number "1.5" is chosen to define equivalence for both the micturition and incontinence parameters. This number may be appropriate for the analysis of micturition because baseline micturition is approximately 11 and endpoints approximately 9 so that 1.5 represents a variation of about $\pm 15\%$. However, baseline incontinence is approximately 3 while endpoints are about 1. This allows for variations of $\pm 50\%$. This amount of variation is too wide to reasonably conclude equivalence.**
- 3. Mean volume voided is an objective physiologic parameter. Both tolterodine and the active control beat placebo with increased bladder volume. It appears, however, that the active drug response is greater than tolterodine. The sponsor's analysis reveals that tolterodine and the active control are not statistically different in their response. This type of analysis does not prove equivalence.**

Safety Deficiencies:

- 1. It would have been appropriate for ECG measurements to be taken within the 12 week study period. Data from follow-up ECG's will be examined for safety problems when all safety data is examined later in this review.**
- 2. Residual urine should have been measured at some point during the study period.**

5.0 Clinical trial CTN 94-OATA-009 (Part A)

5.1 Design and conduct of trial: This was a multicenter, multinational, randomized, double-blind, placebo controlled trial comparing tolterodine 1mg. b.i.d., tolterodine 2mg. b.i.d. and placebo. Three hundred sixteen patients were randomized to treatment at 25 centers (18 in the USA and 7 in Australia). The first patient was recruited on 11 September 1995 and last patient completed assessments of Oct. 8, 1996. Patients were randomized after a two week wash-out period to a twelve week study. Those who completed the 12 week study are invited to participate in an open label long term follow up study involving treatment with tolterodine 2mg. bid for 9 months (CTN 94 OATA-009 [Part B]).

Male and female patients over 18 years of age with detrusor instability were included in the study. Detrusor instability was demonstrated urodynamically by a detrusor contraction of equal to or more than 10 cm. of water during cystometry. No drugs affecting bladder function were permitted within 7 days of urodynamic investigation. During the run-in period, patients were required to have symptoms of urinary frequency defined as at least 8 micturitions on average per 24 hours. In addition patients were required to have symptoms of urge incontinence (at least one episode of incontinence on average per 24 hours) during the run-in period or urinary urgency or both. Patients were excluded if they had significant stress incontinence. Patients were additionally excluded if they had residual volumes of more than 200 ml, had a history of interstitial cystitis or had a total voided volume of more than 3000 ml on average per 24 hours.

Reviewer's comment:

- 1. Patients with neurological disease are not specifically excluded from this protocol however, a "patient with any disease which in the opinion of the investigator makes the patient unsuitable for inclusion" is excluded. It is unclear what this means.**

Following completion of a washout/run-in period (one week for naïve patients and two weeks for patients who had been on anti-incontinence medication), patients were randomized at visit 2 (day 1) to tolterodine 1 mg. bid, tolterodine 2 mg bid or placebo. The randomization occurred in the ratio of 2:2:1.

The study period lasted 12 weeks. Patients were seen and evaluated at week 2 (visit 3), week 4 (visit 4), week 8 (visit 5) and week 12 (visit 6). There was a follow-up visit at least 2 weeks after visit 6 for assessment of adverse events. At the termination of the controlled study the patients were given the option to enter an open label safety study (94-OATA-008 part B) of tolterodine 2mg bid for 9 months.

A computer generated randomization list was prepared by the sponsor using the method of random permuted blocks within centers. The block size was five. Patients who completed the wash-out/ run-in period and were eligible for the study were randomized to treatment with tolterodine 1 mg, tolterodine 2 mg or placebo in the ratio 2:2:1 in

accordance with the randomization list. The patient numbers had five digits. The first three digits identified the center and the last two digits identified patients randomized consecutively at the center. Informed consent was obtained before randomization. The code could only be broken for medical necessity and in this case the situation was to be reported to the sponsor within 24 hours. Tolterodine 1 mg and 2 mg tablets appeared the same except the 1mg tablets had OT inscribed on them while the 2mg tablets had DT inscribed on them. The placebo tablets are said to be "physically indistinguishable" from the tolterodine tablets.

Reviewer's comment: The two doses of tolterodine can be distinguished from each other. Therefore placebo cannot be exactly the same as the active medication. This could cause some bias among patients and investigators.

Patients took tolterodine 1 mg bid (one x 1mg tablet twice daily) or 2 mg bid (one 2 mg tablet bid) or placebo (one tablet twice daily). Patients were instructed to take the tablets whole with half a glass of water in the morning and the evening. Dose reduction was not permitted.

The primary efficacy variable was the change in mean number of micturitions per 24 hours. A micturition chart printed in intervals of one hour was used to collect efficacy data. During the 7 day period preceding visit 2, 3, 4, 5, and 6 patients recorded the time of each spontaneous micturition, each incontinent episode and the number of pads used per 24 hours. The volume voided at each micturition was noted during 2 of the 7 day recording period. The secondary efficacy variables were the change in mean number of incontinence episodes per 24 hours, the change in mean volume voided per micturition, the number of pads used per 24 hours and the patient's perception of bladder condition.. Only complete data for full 24 hour days were included in the calculation of the micturition parameters. Data obtained during any period of a confirmed urinary tract infection were excluded from the data.

Clinical safety assessments included ECG (measured at baseline and visit 12 or at time of withdrawal), BP within 6 hours of drug intake at visit 2,4 and 6 and residual urine measured at baseline and if the patient experienced symptoms of retention during the study.

Reviewer's comment:

1. Residual urine should have been measured at some point during the study period.

Adverse events were monitored in the routine fashion.

Laboratory safety assessments for routine blood laboratory tests were obtained at visit 1, 4, and 6 or at withdrawal. Samples were analyzed at a central laboratory. A midstream specimen of urine was obtained at visit 1.

Reviewer's comment:

1. **A urine specimen should have been obtained during the study period to determine if asymptomatic urinary tract infection is more common in the drug groups.**

Drug serum concentrations of tolterodine and DD 01 (major active metabolite) were obtained at visit 1, 4, 6 or withdrawal within 6 hours of ingestion of the study drug. Analysis was done at a central laboratory.

5.2 Study population: The intent-to-treat (ITT) population included all patients randomized to the study. The only criterion for exclusion from the ITT population was not ingesting any medication. The per-protocol population (PP) included all randomized patients who had completed the study without violating any major eligibility or protocol criteria. Patients who were withdrawn from treatment or who had dose reductions were excluded from the PP population. The safety population included those patients that were randomized and received at least one dose of study medication (the same as the ITT population). Table 12 illustrates the relationship between the ITT and PP populations.

Table 12
Number of Patients in Intent-to-Treat (ITT) and Per-Protocol (PP) Population
(Study CTN 94-OATA-009)

	Tolterodine 1mg	Tolterodine 2 mg	Placebo	Total
ITT (N)	123	129	64	316
PP n, (n/N)	78, (63%)	89, (69%)	40, (67%)	201, (64%)

A total of 316 patients were randomized to treatment. Sixty-four patients received placebo, 123 tolterodine 1mg and 129 tolterodine 2 mg. In the ITT population there were no statistically significant differences with respect to baseline demographic characteristics. Approximately 70% of each group was female. Caucasians accounted for 93% of the ITT group. The mean age was approximately 60 years while the mean body mass index was about 27 kg/m².

Baseline parameters related to disease characteristics were similar among the three groups. Over 50% of patients had symptoms of urgency for over 5 years. Approximately 50% of the patients had previously taken drugs for urge incontinence and 33% had had surgery affecting the lower urinary tract. Micturition chart variables and urodynamic variables were similar among the three groups.

Many patients had concurrent disease with hypertension (8%) and arthritis (4%) being the most common. Because of this, most of the patients (93%) were receiving medication for other disease states. These medications represented a wide variety of drug groups.

Reviewer's comment:

1. **Some adverse events observed in this study may represent disturbances in the cytochrome p450 system precipitated by enzyme deficiencies in patients or drug/drug interaction. A more complete comment on this subject will be made in the Safety review of all studies**

5.3 Withdrawals and compliance: A patient was withdrawn from treatment if the investigator felt it was medically necessary or the patient requested it. Twenty-five patients withdrew from the study. Three(5%) from the placebo group, 7 (6%) from the tolterodine 1 mg group and 15 (12%) from the tolterodine 2 mg group. This did not represent a significant difference between treatment groups. The most common reason for withdrawal was adverse events. The most common adverse events were visual accommodation problems and dry mouth.

Compliance was checked by tablet count of returned medication at visit 4,5,and 6. There was additional confirmation of compliance by analysis of serum concentrations of tolterodine and its metabolite at visit 4 and 6. Patients were directly asked if they were having trouble with compliance and this was recorded in the CRF.

5.4 Protocol violations and deviations: Eighty-nine patients (28%) had major protocol violations. There were 21 (33%) patients in the placebo, 38 (31%) patients in the tolterodine 1 mg and 30 (23%) patients in the tolterodine 2 mg groups with at least one major protocol violation. The most common protocol violations were prohibited concomitant medication and non-compliance. There appeared to be fairly even distribution of these violations between the various groups. There were three patients that were randomized but never dosed. Two were assigned to the tolterodine 1 mg group and the other to the tolterodine 2mg group. These patients were not included in any analysis.

There were several protocol deviations that altered the conduct and analysis of the study from the original protocol.

Reviewer's comment:

1. **The protocol deviations did not substantially affect the conduct or outcome of the study.**

5.5 Efficacy analysis

5.51 Statistical Methods: Differences between means and changes from baseline to endpoint are compared to show differences with a level of $P \leq 0.05$ considered to be significant.

When equivalence is determined, 95% confidence intervals are employed. Confidence intervals of ± 1.5 are used for both the micturition and incontinence variables.

Reviewer's comment: