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 ± 15%. However, baseline incontinence per 24 hours is approximately 3 while endpoint is about 1. This allows for variations of ± 50%. This amount of variation is too wide to reasonably conclude equivalence.**

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.

5.52 Efficacy Results: : The primary parameter of the study was the comparison of the effect of treatment with tolterodine 1 mg and 2mg relative to placebo on micturitions per 24 hours. See table 13 and 14

Table 13
Mean Number of Micturitions per 24 Hours at Baseline and Endpoint (week 12)
Study- CTN 94-OATA-009 (ITT)

	Placebo	Tolterodine 1mg	Tolterodine 2 mg
Baseline	11.3	11.5	11.2
Endpoint	9.9	9.2	9.0
Change	-1.4	-2.3	-2.3
P	<0.0001	<0.0001	<0.0001

Table 14
Change from Baseline to Endpoint (week 12) in Mean Number in Micturitions per 24 Hours, Comparative Analysis
Study- CTN 94-OATA-009 (ITT)

	Tolterodine 1mg vs. Placebo	Tolterodine 2mg vs. Placebo
Base to End	0.9	0.9
95% CI	-1.6,-0.3	-1.5, -0.3
P	0.0029	0.0045

The PP analysis for the change from baseline to endpoint between the tolterodine groups and placebo was similar but the results did not show the same degree of statistical

significance. The p values for the comparison with tolterodine 1mg and 2mg with placebo were 0.043 and 0.053 respectively.

Reviewer's Comment:

1. **The change from baseline to endpoint for both the tolterodine groups is approximately a decrease of 1 micturition per 24 hours over placebo. The absolute change is approximately 2.3 including the placebo effect. The patients have 11.5 micturitions per 24 hours at baseline and thus experience an improvement of about 9% due to tolterodine.**

Important secondary parameters were mean incontinence episodes per 24 hours and mean volume voided per micturition. Tables 15, 16,17 and 18 display these results.

Table 15
Mean Number of Incontinence Episodes per 24 Hours at Baseline and Endpoint (12 weeks)
Study- CTN 94-OATA-009(ITT)

	Placebo	Tolterodine 1mg	Tolterodine 2mg
Baseline	3.5	3.9	3.6
Endpoint	2.2	2.2	1.8
Change	-1.3	-1.7	-1.7
P	0.0003	0.0001	0.0001

Table 16
Change from Baseline to Endpoint (week 12) in Mean Number of Incontinence Episodes per24 Hours, Comparative Analysis
Study- CTN 94-OATA-009 (ITT)

	Tolterodine 1mg vs. Placebo	Tolterodine 2mg vs. Placebo
Base to End	-0.4	-0.4
95% CI	-1.0, 0.3	-1.1, 0.2
P	0.27	0.19

Urinary incontinence was not an entry requirement for the study. The patients could have either urgency or urge incontinence. A total of 35 patients were excluded from this analysis because they did not have incontinence at baseline. Fourteen percent of the placebo group, 11% of the tolterodine 1 mg group and 9% of the tolterodine 2mg group were excluded. The PP group was then constructed in the same manner as previously mentioned. The per protocol analysis indicated similar results as the ITT analysis.

Reviewer's comments:

1. **In the ITT and PP populations tolterodine is not superior to placebo in improving incontinence episodes. The sponsor stated that the study was not powered to detect differences in incontinence.**

Table 17
Mean Volume voided per Micturition(ml) at Baseline and Endpoint (12 weeks)
Study- CTN 94-OATA-009 (ITT)

	Placebo	Tolterodine 1mg	Tolterodine 2mg
Baseline	158	151	155
Endpoint	168	178	190
Change	10	27	36
P	0.091	0.0001	0.0001

Table 18
Change from Baseline to Endpoint (week 12) in Mean Volume Voided (ml) per Micturition, Comparative Analysis
Study- CTN 94-OATA-009 (ITT)

	Tolterodine 1mg vs. Placebo	Tolterodine 2mg vs. Placebo
Base to End	17	26
95% CI	5, 29	14, 38
P	0.0059	<0.0001

In the placebo group the change from baseline to week 12 was not statistically significant. In both tolterodine groups there is a statistically significant increase from baseline to endpoint in mean volume voided per micturition. There is also a statistically significant difference between the placebo group and both tolterodine groups with respect to this change. In the per protocol population, there was no statistically significant difference in this parameter between the tolterodine 1 mg group and placebo. However, the comparison with the tolterodine 2 mg group and placebo was significant.

Reviewer's comments:

1. **Mean volume voided is an objective physiologic parameter. Both tolterodine 1mg and 2 mg were more effective than placebo in producing increased bladder volume in the ITT analysis.**

Another secondary parameter was patients' perception of bladder condition. This parameter was measured by a six-point rating scale. At the end of the study, 59% of the patients in the tolterodine 2mg group, 41% of the patients in the tolterodine 1 mg group and 38% of the placebo patients showed subjective improvement in perception of their bladder condition. The difference between the tolterodine 2mg and placebo group were statistically significant but not between the tolterodine 1mg and placebo groups.

Reviewer's comment: This scale has not been tested for reliability or validated and therefore cannot support efficacy claims.

5.6 Safety analysis

Deaths: One patient died during the study (#90110). The patient who experienced an exacerbation of congestive heart failure was assigned to the placebo group.

Serious adverse events: Serious adverse events were reported for 13 patients, one in the placebo group, 5 in the tolterodine 1 mg group and 7 in the tolterodine 2 mg group. Except for one patient the medication was continued and the patients remained in the study. The investigators believed that two of the events were possibly related to study medication.

Review of the case histories by the Division, confirmed the assessment of the investigators that the other 11 events unlikely to be related to the drug treatment. The 2 patients that had adverse event possibly related to the drug were patient 90008 (cerebrovascular disorder) and patient . Patient had a left cerebrovascular accident with ultimate full recovery. The patient's neurologist allowed the patient to continue in the study. Patient was ultimately diagnosed as a cerebrovascular accident and recovered with some disability. This was the only patient not continued in the study. The relationship of these two adverse events and drug administration is unclear.

All adverse events:

Fifty (78%) patients in the placebo group, 90 (74%) in the tolterodine 1 mg group and 93 (73%) in the tolterodine 2mg group experienced adverse events. the most common adverse event in the tolterodine groups was dry mouth (see table 19).

Table 19
Proportion of Each Treatment Group that Reported Dry Mouth at Least Once in Study CTN 94-OATA-009 (Part A)[a]

	Placebo	Tolterodine 1 mg	tolterodine 2 mg
Per cent	13	24	39

a. Tolterodine 1mg vs. placebo(p=0.071), tolterodine 2mg vs. placebo (p<0.001), tolterodine 1mg vs. tolterodine 2 mg (p=0.009).

Laboratory and clinical safety parameters: There was a statistically significant decrease in systolic blood pressure (-3 mm Hg,p=0.033) from baseline to week 12 in the tolterodine 2 mg group. There were no significant changes in the tolterodine 1 mg or placebo group. There was a statistically significant decrease in diastolic blood pressure (-2 mmHg,p=0.019) in the tolterodine 2 mg group. There were no significant changes in the placebo or tolterodine 2 mg groups.

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

EKG changes between visit 2 and 6 which were judged to be clinically significant occurred in 2 palcebo,1 tolterodine 1mg patient and 2 tolterodine 2 mg patients. These were all reported as adverse events. The events were rated mild to moderate and felt to be unlikely related to the study medication by the investigator.

Blood samples for determination of serum tolterodine and DD01 were drawn 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 240(95%) of the tolterodine patients and a total of 12(5%) patients were classified as PMs.

5.7 **Reviewer's assessment of safety and efficacy**

The sponsor concludes that tolterodine is safe and generally well tolerated. Tolterodine 1mg and 2mg were significantly more effective than placebo with respect to reducing mean micturitions per 24 hours from baseline to12 weeks. In addition both doses significantly increased mean volume voided per micturition from baseline to week 12 compared to placebo. Neither tolterodine dose reduced the mean number of incontinence episodes compared to placebo.

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. Tolterodine 1mg does not appear to be significantly different from tolterodine 2 mg for efficacy or safety parameters. 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).

Efficacy deficiencies:

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.**

2. **The two doses of tolterodine can be physically distinguished from each other. Therefore placebo cannot appear exactly the same as the active medication. This could cause some bias among patients and investigators due to lack of blinding.**

3. **It is unclear why the number "1.5" was 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 ± 15%. However, baseline incontinence per 24 hours is approximately 3 while endpoints are about 1. This allows for variations of ± 50%. This amount of variation is too wide to reasonably conclude equivalence.**

4. **In the ITT and PP populations tolterodine is not superior to placebo in improving incontinence episodes It is of some concern that tolterodine did not beat placebo in this parameter in this study.**

5. **The disease specific "quality of life" scales were not tested for reliability or validated and therefore cannot support efficacy claims.**

Safety Deficiencies:

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

2. **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.**

3. **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.**

6.0 Clinical trial CTN 94-OATA-010 (Part A)

6.1 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 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]).

Male and female patients over 18 years of age with detrusor overactivity were included in the study. Detrusor overactivity 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 or "any disease which in the opinion of the investigator would make the patient unsuitable for entry". 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 are 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-010 part B).

In the case of intolerance to the study drug and only as an alternative to withdrawal, an option of dose reduction was available. The reduction was made no later than visit 3. In these cases the following dose reductions were permitted. In these cases patients took two tablets b.i.d. rather than two tablets t.i.d. Dose escalation following dose reduction was not permitted. Reduced dose schedule is as follows:

1. One tolterodine 1 mg tablet bid (morning and evening) plus one placebo oxybutynin tablet bid.

2. One oxybutynin 5 mg tablet bid and one placebo tolterodine tablet bid

3. One placebo tolterodine tablet bid and one placebo oxybutynin tablet bid.

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 "Initial dose" or "Reduced dose."

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 changes in mean number of micturitions 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, an SF-36 index, and a disease specific 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 if the patient experienced symptoms of retention during the study.

Reviewer's comments:

1. **It would have been appropriate for ECG measurements to occur within the 12 week study period because comparison with follow-up ECG may have yielded useful information.**

2. **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. 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.

6.2 Study Population: The intent-to-treat (ITT) population included all patients randomized to the study who had taken one dose of study 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 20 illustrates the numerical relationship between the ITT and PP populations.

Table 20
Number of Patients in Intent-to-Treat (ITT) and Per-Protocol (PP)Population
(Study CTN 94-OATA-010)

	Tolterodine	Oxybutynin	Placebo	Total
ITT (N)	108	111	55	274
PP n, (n/N)	70, (65%)	41, (37%)	36, (65%)	147, (54%)

A total of 274 patients were randomized to treatment and took one dose of study medication. There were three patients (one in each group) who were randomized but did not take one dose of study medication. Fifty-five received placebo, 108 tolterodine and 111 oxybutynin. In the ITT population there were no statistically significant differences with respect to baseline demographic characteristics. Approximately 75% of each group was female. About 92% were Caucasians the rest were Black, Asian or Hispanic. The mean age was approximately 64 years while the mean body mass index was about 28 kg/m^2.

Baseline parameters related to disease characteristics were essentially similar among the three groups. Approximately 45% of patients had symptoms of urgency for over 5 years. Approximately 50% of the patients had previously taken drugs for urge incontinence and 35% had had surgery affecting the lower urinary tract. Micturition chart variables and urodynamic variables were similar among the three groups. Approximately 6% of the patients had neurological disease as they were classified as having hyperreflexia as opposed to detrusor instability. Three (5%) were in the placebo group, 8 (7%) in the tolterodine group and 8 (7%) in the oxybutynin group.

There was a significant difference (p=.019) among the groups with respect to the proportion of patients that had undergone previous surgery of the urinary tract. More patients in the oxybutynin group (45%) than in the tolterodine group(27%) or the placebo group (34%) underwent such surgery.

The majority of patients in all groups had concurrent disease with hypertension (9%), postmenopausal disorders (6%) and arthritis(7%) being the most common. Because of this, most the of patients in each group (93%) were taking concomitant medication during the study. These medications represented a wide variety of drug groups.
Reviewer's comment: 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.

6.3 Withdrawals and compliance: A total of 57 patients were withdrawn from the study. This included the one patient in each group that was withdrawn because no study medication was taken. There were 8 (14%) placebo patients, 14 (13%) in the tolterodine

group and 35 (31%) in the oxybutynin group that were withdrawn from the study. The proportion of treatment withdrawals was significantly higher in the oxybutynin group than the tolterodine ($p<0.001$) or placebo ($p=0.018$) groups.

Reasons for withdrawal were primarily adverse events. Only one patient in the tolterodine group and 2 in the oxybutynin group were lost to follow-up. No placebo patients were lost to follow-up. Thirty-four out of 57 patients that withdrew did so because of adverse events (60%). Dry mouth was the most common type of adverse event. It was reported by 15% of the placebo group, 30% of the tolterodine group and 69% of the oxybutynin group (tolterodine vs. placebo, $p=0.034$; oxybutynin vs. placebo, $p<0.001$: oxybutynin vs. tolterodine, $p<0.001$). Dry mouth was the cause for withdrawal in 1 out of 8 (13%)of the placebo group, none of the tolterodine group and 10 out of 35 (29%) of the oxybutynin group.

Compliance was calculated on basis of the number of returned tablets versus the number of delivered tablets. Patients who took at least 86% of the study medication were considered compliant. Eighty-four per cent of the placebo group, 83% of the tolterodine group and 72% of the oxybutynin group were judged to be compliant.

6.4 Protocol violations and deviations: A total of 71/274 patients (26%) had at least one major protocol violation. Fifteen out of 55 in the placebo group(27%), 24/108 (22%) in the tolterodine group and 32/111 (29%) in the oxybutynin group had these violations. Patients who had violations were included in the ITT but excluded from the PP analysis. The most common violation was non compliance. This accounted for 5/16 (31%) of the violations in the placebo group,13/26 (50%) in the tolterodine group and 8/3(23%) in the oxybutynin group. Other common violations were "no valid urodynamic data at entry" and "no valid micturition chart data at week 12."

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 who could not tolerate the standard dose. Thirty-six out of 274 (13%) patients in the study were in this category. There were 2/272 (1%) in the placebo group, 8/274 (3%)in the tolterodine group and 26/274(9%) in the oxybutynin group.

6.5 Efficacy analysis

6.51 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:

1. **It is unclear why the number "1.5" was 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 ± 15%. However, baseline incontinence per 24 hours is approximately 3 while endpoint is about 1. This allows for variations of ± 50%. This amount of variation is too wide to reasonably conclude equivalence.**

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.

In this study a small number of patients recorded a large number of incontinence episodes. Therefore if a patient had more than 24 episodes per 24 hours it was given a value of 24 in the statistical analysis.

6.52 Efficacy Results: The primary parameter 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 21, 22 and 23.

Table 21
Mean Number of Micturitions per 24 Hours at Baseline and Endpoint (week 12)
Study- CTN 94-OATA-010 (ITT)

	Placebo	Tolterodine	Oxybutynin
Baseline	11.6	11.6	11.5
Endpoint	10.2	9.9	9.8
Change	-1.4	-1.7	-1.7
P	0.0007	0.0001	0.0001

Table 22
Change from Baseline to Endpoint (week 12) in Mean Number in Micturitions per 24 Hours Comparative Analysis
Study- CTN 94-OATA-010 (ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-0.4	-0.4	0.0
95% CI	-1.0,0.3	-1.0,0.3	-0.6,0.5
P	0.27	0.29	

Table 23
Change from Baseline to Endpoint (week 12) in Mean Number of Micturitions per 24 Hours
Study- CTN 94-OATA-010 (PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-0.9	-0.8	0.0
95% CI	-1.7, -0.1	-1.8,0.0	-0.6, 0.5
P	0.036	0.066	

Reviewer's comments:

1. **The data indicate that in the ITT population there is no difference between placebo and either active treatment group in change from baseline to endpoint in mean micturitions per 24 hours. The results of the PP population are similar to the ITT except that there was a statistically significant difference between placebo and tolterodine with respect to change from baseline to week 12 for micturitions per 24 hours.**

Important secondary parameters were mean incontinence episodes per 24 hours and mean volume voided per micturition. Table 24-29, display these results. Not all patients who entered the study had incontinence at baseline. The number of patients that had incontinence at baseline is illustrated in table 24.

Table 24
Mean Number of Incontinence Episodes per 24 Hours at Baseline and Endpoint (12 weeks)
Study- CTN 94-OATA-010 (ITT)

	Placebo (n=50)	Tolterodine (n=91)	Oxybutynin (n=103)
Baseline	3.5	3.7	3.4
Endpoint	2.4	2.1	1.5
Change	-1.1	-1.6	-1.9
P	0.0006	0.0001	0.0001

Table 25
Change from Baseline to Endpoint (week 12) in Mean Number of Incontinence Episodes per24 Hours
Study- CTN 94-OATA-010(ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-0.5	-0.8	0.3
95% CI	-1.1,0.1	-1.4,-0.2	-0.2,0.8
P	0.13	0.012	

Table 26
Change from Baseline to Endpoint (week 12) in Mean Number of Incontinence Episodes per24 Hours
Study- CTN 94-OATA-010(PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	-.7	-0.7	0.0
95% CI	-1.4,0.0	-1.5,0.1	-0.7, 0.7
P	0.063	0.10	

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 33 patients were excluded from this ITT analysis because they did not have incontinence at baseline. Eleven percent of the placebo group, 17% of the tolterodine group and 8% of the oxybutynin group were excluded. The PP group was then constructed the same manner as previously mentioned.

Reviewer's comments:

1. **In the ITT analysis there is no significant difference between placebo and tolterodine in change from baseline to endpoint in mean incontinence episodes per 24 hours. However, there is statistically significant difference between oxybutynin and placebo. This would indicate that this study was sensitive enough to detect a treatment effect and that tolterodine failed to demonstrate one. In the PP population, neither active drug was statistically different from placebo.**

2. **The sponsor states that tolterodine and the active control are "equivalent." However, it is unclear what this means when tolterodine does not demonstrate a treatment effect.**

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 27,28 and 29.

Table 27
Mean Volume voided per Micturition(ml) at Baseline and Endpoint (12 weeks)
Study- CTN 94-OATA-010 (ITT)

	Placebo	Tolterodine	Oxybutynin
Baseline	160	155	149
Endpoint	173	186	195
Change	13	31	46
P	0.060	0.0001	0.0001

Table 28
Change from Baseline to Endpoint (week 12) in Mean Volume Voided (ml) per Micturition
Study- CTN 94-OATA-010 (ITT)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	17.8	32.8	-15.0
95% CI	3.5,32.1	18.6, 47.0	-26.7,-3.3
P	0.015	0.0001	0.012

Table 29
Change from Baseline to Endpoint (week 12) in Mean Volume Voided (ml) per Micturition
Study- CTN 94-OATA-010 (PP)

	Tolterodine vs. Placebo	Oxybutynin vs. Placebo	Tolterodine vs. Oxybutynin
Base to End	22.0	38.6	-16.7
95% CI	5.9, 38.0	20.8, 56.5	-32.0, -1.3
P	0.0075	0.0001	0.034

Reviewer's comment:

1. **Mean volume voided is an objective physiologic parameter. Both the active control drug and tolterodine had a statistically significant increase in mean voided volume compared to placebo. However the active control is significantly better in increasing bladder capacity than tolterodine.**

There were no clinically meaningful differences between the groups in quality of life and patient perception scales.

6.6 Safety analysis

Deaths:
There were no deaths during this study.

Serious or severe adverse events:
Serious adverse events were reported in 6 patients. Two out of 55 patients (4%) in the placebo group, 1/108 (1%) in the tolterodine group, and 3/111(3%) in the oxybutynin group. Three patients had serious adverse events and discontinued the study while the remaining three continued in the study. The investigators and sponsor believed that the adverse events were not related to study drug. After reviewing the case histories, the reviewer agrees with their assessment. All the patients in this category had significant concurrent disease such as diabetes and hypertension.

All adverse events:
A total of 108 AE's was reported by 41 (75%) of patients in the placebo group, 234 AE's were reported by 84 (74%) of patients in the tolterodine group and 342 AE's reported by 100 (90%) of the patients in the oxybutynin group. The most frequently reported AE's were autonomic nervous system disorders (dry mouth, accommodation, anorexia) of these the most common was dry month.

Dry mouth was reported by 8 (15%) of the patients in the placebo group,32(30%) of the patients in the tolterodine group and 77 (69%) of the patients in the oxybutynin group (see table 30). Two (4%) of the placebo group, 8(7%) of the tolterodine group and 26 (23%) of the patients required dose reduction due to AE's (mainly dry mouth). The proportion of patients that required dose reduction was significantly higher in the oxybutynin group than the tolterodine group ($p<0.001$). A higher proportion of patients in the tolterodine group than placebo patients required dose reduction ($p<0.001$)

Cardiovascular events occurred in no patient in the placebo group, one patient (1%) in the tolterodine group and two patients (2%) in the oxybutynin group.

Table 30
Proportion of Each Treatment Group that Reported Dry Mouth at Least Once in Study CTN 94-OATA-010 (Part A)[a]

	Placebo	Tolterodine	Oxybutynin
Per cent	15	30	69

a. Tolterodine vs. placebo ($p=0.034$), oxybutynin vs. placebo and oxybutynin vs. tolterodine ($p< 0.001$)

Laboratory and clinical safety parameters:
There was no significant change from baseline to endpoint in either **systolic** or **diastolic blood pressure.**

There were some statistically significant changes in **chemistry and hematology** parameters from baseline to week 12 but there did not appear to be a clinically significant trend.
Reviewer's comment: A larger safety base will be reviewed 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 later in this review for safety problems.

Blood samples for determination of serum tolterodine and DD01 were drawn 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 104(95%)of the tolterodine patients and 5(5%) of those were found to be PM's.

6.7 Reviewers assessment of safety and efficacy: The sponsor concludes that tolterodine is 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 is less with tolterodine compared to oxybutynin. The sponsor believes that tolterodine and oxybutynin were equivalent with respect to reduction in the mean number of micturitions and incontinence episodes per 24 hours. However, the active groups were not better than placebo in treatment response. Tolterodine and oxybutynin resulted in a statistically significant increase in volume voided relative to placebo.

The Division substantially agrees with the sponsor's assessment of the study. In the PP but not the ITT population tolterodine is better that placebo in reducing mean micturitions per 24 hours. Tolterodine is not better than placebo in reducing mean incontinence episodes per 24 hours in either population. The effect of tolterodine on voided volume lends support to the claim that it is effective in overactive bladder. There is also convincing evidence that tolterodine will be better tolerated than oxybutynin. However, the fact that the tolterodine group does not produce a treatment in the ITT population for either reduction of micturition or incontinence episodes is of concern. The fact that tolterodine is equivalent to oxybutynin in this situation is of questionable significance.

There is some question as to whether any indication is supported by this study. In addition, however because the study had only a small number of patients with neurologic disease the sponsor's proposed label is not supported by this study. The proposed label states that "Detrusitol (tolterodine) tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence or any combination of these symptoms." Overactive bladder refers to all types of bladder hyperactivity. However in this study only 19 (7%) of patients had "detrusor hyperreflexia" the rest had "detrusor instability." If one accepts the evidence from the PP analysis that tolterodine is effective in the reduction of mean number of micturitions pr 24 hours and that there is no evidence that tolterodine is effective in reducing incontinence episodes then the label would read as follows: Tolterodine tablets are indicated for the treatment of patients with detrusor instability with symptoms of urinary frequency.

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

Efficacy deficiencies:

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 as to what this means.

2. **Patients were not blinded as to whether they received "study" or "reduced" dose. This might alter efficacy or safety parameters.**

3. **It is unclear why the number "1.5" was 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 ± 15%. However, baseline incontinence per 24 hours is approximately 3 while endpoint is about 1. This allows for variations of ± 50%. This amount of variation is too wide to reasonably conclude equivalence.**

4. **The Data indicates that in the ITT population there is no difference between placebo and either active treatment group in change from baseline to endpoint in mean micturitions per 24 hours. The sponsor maintains that "equivalence" is demonstrated between the two active arms. The results of this study do seem to demonstrate statistical equivalence of the two active arms. However, because there is no treatment effect these results are not clinically meaningful.**

5. **In the ITT analysis there was no significant difference between placebo and tolterodine in change from baseline to endpoint in mean incontinence episodes per 24 hours. However, there is statistically significant difference between oxybutynin and placebo. This would indicate that this study was sensitive enough to detect a treatment effect and that tolterodine failed to demonstrate one. In the PP population, neither active drug was statistically different from placebo.**

6. **Mean volume voided is an objective physiologic parameter. Both the active control drug and tolterodine had a statistically significant increase in mean voided volume compared to placebo. However the active control was significantly better in increasing bladder capacity than tolterodine.**

<u>Safety Deficiencies:</u>

1. **It would have been appropriate for ECG measurements to occur within the 12 week study period because comparison with follow-up ECG may have yielded useful information. Increased residual urine could be an etiologic factor in urinary tract infections.**

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

3. **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.**

7.0 Supportive Study CTN 94-OATA-015 (Part A)

This is a multicenter, multinational (Netherlands, France, Switzerland), randomized, double-blind, double-dummy, active-controlled study in 240 patients with detrusor overactivity. Patients were randomized to treatment with tolterodine 2 mg bid plus placebo oxybutynin or oxybutynin 5 mg po tid plus placebo tolterodine for twelve weeks. Eligible patients who completed the full study period were allowed to participate in an open label nine month safety extension with tolterodine 2 mg bid. The conduct of this study is similar to the previously discussed placebo controlled 12 week studies. The study was conducted from June 1995 to August 1996.

The primary endpoint is reduction in mean micturitions per 24 hours from baseline to 12 weeks. Secondary endpoints are reduction in mean incontinence episodes per 24 hours and change in mean volume voided per micturition over the same time period. Approximately 70% of the patients were female, 95% caucasian and 6% of the patients had bladder instability on the basis of neurologic disease. The study was designed as an "equivalence study" with 95% confidence intervals of ± 1.5 for both mean micturitions per 24 hours and mean incontinence episodes per 24 hours.

The baseline mean micturitions per 24 hours were 12 for both tolterodine and oxybutynin groups. The two groups had a statistically significant (p=0.0001) decrease from baseline in **mean micturitions per 24 hours** (-2.1 tolterodine -2.7 oxybutynin). The groups were demonstrated to be equivalent for the ITT population (tolterodine vs. oxybutynin: 0.58, 95%CI -0.15 to 1.31). However if one patient on oxybutynin who was found to have a urinary tract infection and was voiding 59 times per day at week two (this last observation was carried forward as the patient was subsequently dropped from the trial) is excluded, the drugs are not equivalent (tolterodine vs. oxybutynin: 0.97, 95% CI, 0.42 to 1.52).

The mean number of incontinence episodes per 24 hours at baseline was 4.8 for the tolterodine group and 4.3 for the oxybutynin group. In the ITT population both groups had a statistically significant (p=0.0001) decrease from baseline to week twelve in **mean incontinence episodes per 24 hours** (-1.7 tolterodine -2.1 oxybutynin). The groups were equivalent with respect to mean change (tolterodine vs. oxybutynin: 0.41 , 95% CI, -0.23 to 1.06).

The mean volume voided per micturition at baseline was 153 ml for tolterodine and 142 for oxybutynin. Both groups had a statistically significant increase (p=0.0001) from baseline to week 12 in mean volume voided per micturition (tolterodine 35 ml, oxybutynin 54 ml).
However, the increase in **mean volume per micturition** was greater in the oxybutynin than the tolterodine group (p=0.0032).

Safety parameters were similar to the other 12 week studies reviews above. **Dry mouth** was the most commonly reported adverse event in each group (38% tolterodine, 78% oxybutynin). The difference was statistically significant (p<0.001).

Reviewer's comments:

1. **The statement that tolterodine and oxybutynin are equivalent is only weakly supported by the data from this study.**

2. **Many of the deficiencies that are mentioned with respect to the reviewed placebo controlled trials are applicable to this active controlled study.**

8.0 Safety Update Report

A 4-month safety update was submitted on 7/14/97 and reviewed as part of the reviewer's assessment of safety. A second safety update (8.5 month safety update) was sent to the division on 12/31/97 and is reviewed here. It contains safety information for patients who participated in the tolterodine clinical program through 12/9/97. Since the 4-month update the number of patients eligible for 6 month analysis increased by 1.5% (to 1670 patients) while the number of patients eligible for 13 month analysis increased by 60% (to 1296 patients)

Deaths: There were four deaths during this update period for patients who had been on tolterodine at least 12 months. The investigators judged these deaths to be unlikely related to tolterodine. The reviewer agrees with this assessment after reading the medical summaries and related material.

Serious Adverse events: The incidence of serious adverse events in the 6 and 12 month populations was 10.1% versus 8.1% in the first update and 10.0% in the ISS. Review of the adverse event profile reveals that it is similar to the previous update with some additional unrelated events. Cardiac events are analyzed as a subgroup. There appear to be no significant changes in the incidence or profile of cases that would signal increased cardiac events.

All adverse events: A table listing all adverse events at a cumulative incidence of 1% or greater in the current update, the 4-month update and the ISS was reviewed. There were no significant changes in incidence or profile of the events.

9.0 Reviewer's assessment of safety and efficacy of tolterodine

Safety: The safety review of the submitted NDA was based on two data sets. The short term experience (up to 12 weeks) includes approximately 1600 patients who took tolterodine during phase 2 and 3 trials and long term experience includes 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.

In the short term data base, the incidence of serious adverse events in the tolterodine treated patients (3.7%) did not differ from the incidence with the oxybutynin (3.7%) or placebo patients (3.4%). The incidence of serious adverse events reported in the ISS for the long term population was 10% while the proportion of patients reporting serious adverse events in the safety update was somewhat lower (8.1%).

There were four reported deaths in the controlled portion of the studies. One patient had been taking placebo while 3 were on tolterodine. None of the tolterodine deaths were related to the drug. Twelve deaths were reported during the long term, uncontrolled portions of the studies. Eight of these deaths were clearly unrelated to the drug. The other deaths could possibly be related but there were no consistent patterns, no QT prolongation and the deaths were consistent with the patients' age and medical condition. Many of the patients in these studies were of advanced age with multiple medical problems and concomitant medications.

The reviewer believes that there are three areas of concern with respect to 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 although 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. When the data from all studies was reviewed, there was no indication that tolterodine precipitated cardiac events.

As described in section 2.2, tolterodine was metabolized by the cytochrome P450 system. Poor metabolizers were deficient in the 2D6 portion of the system. About 6% of the Caucasian population had 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 or 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.

Efficacy

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 statistically significant efficacy or safety differences between tolterodine 1 and 2 mg were demonstrated. However, there are trends in the data that would indicate tolterodine 2 mg is more active that tolterodine 1 mg. 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 that the mean values. The reviewer believes that this approach may have some validity especially for the incontinence data which tends to have a nonnormal 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.

Overactive bladder is a condition with a continuum of symptoms starting with urgency then frequency and ultimately incontinence. Tolterodine clearly reduced micturition and increased volume voided compared to placebo in the submitted studies. Incontinence was improved but not at a statistically significant level. Because of the nature of this condition, and because of the previously mentioned statistical evidence, the reviewer believes that tolterodine will improve incontinence as well as frequency and urgency in patients with overactive bladder.

In two of the central studies and a supportive study (008,010, 015), oxybutynin 5 mg tid was used an active comparator. In the submitted individual studies, as well as the two "pooled" analyses, oxybutynin tended to demonstrate increased efficacy compared to tolterodine. For example, in two of the studies that included oxybutynin (10 and 15), oxybutynin was better then tolterodine (p=.019 and p=.012) in increasing the volume voided per micturition, a measure of antimuscarinic effect on the bladder. For this reason, the reviewer believes that the decreased "dry mouth" observed in patients taking tolterodine compared to oxybutynin during these trials was likely a result of reduced antimuscarinic effect and thus reduced effectiveness of tolterodine and does not demonstrate 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.

10.0 Recommendation of regulatory action

The reviewer recommends that tolterodine be approved for the indication described above.

10.1 Labeling Revisions; Labeling comments from the reviewer were conveyed at telecons held on 1/6/98 and 1/23/98 as well as IR letters dated 1/16/98 and 1/20/98. The process of labeling revision is ongoing as of the time writing of this review.

3/10/92

Daniel A. Shames MD FACS
Medical Officer, DRUDP /S/

CC/
James Bilstad MD
Lisa Rarick MD
Heidi Jolson MD
Mark Hirsch MD
Alvis Dunson
Division File HFD 580