CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-771

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAR 12 1998

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-771
Compound:	Detrol™ (tolterodine L-tartrate) 1 and 2 mg tablets
Submission Dates:	March 2[illegible],1997 (Original Submission) December 16, 1997 (Amendment Serial No. 008) January 28, 1998 (Amendment Serial No. 012) January 29, 1998 (Amendment Serial No. BB) January 29, 1998 (Amendment Serial No. 013) February 11, 1998 (Amendment Serial No. 015)
Sponsor:	Pharmacia & Upjohn
Type of Submission:	Original NDA (NME)
Code:	1S
Reviewer:	K. Gary Barnette, Ph.D.

I. Synopsis

On March 2, 1997, NDA 20-797 for Detrol™ (tolterodine L-tartrate) was submitted to FDA for the indication of treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Tolterodine is a muscarinic receptor antagonist and is considered a new molecular entity. The proposed dosing regimen is 2 mg twice daily, but may be reduced to 1 mg twice daily based on tolerability. Detrol™ has been formulated into tablets to be orally administered containing 1 and 2 mg of tolterodine.

In response to an Agency request made on December 16, 1997, the sponsor submitted amendment 008 containing a list of the poor metabolizers with adverse events and concomitant medications and extensive metabolizers with serious adverse events and concomitant medications. On January 28 and 29, 1998 the sponsor submitted revised product labeling (Amendment Serial Nos. 012 and BB).

Additionally, on January 29, 1998 and February 11, 1998 the sponsor submitted amendments 013 and 015 which include the preliminary results and summary of Study CTN 97-OATA-036, intended to assess the drug interaction of tolterodine and ketoconazole in poor metabolizers.

In all, the sponsor has submitted 15 pivotal pharmacokinetic studies to support the approval of Detrol™ (tolterodine L-tartrate) for the indication of treatment of overactive bladder. These studies included assessments of single and multiple dose pharmacokinetics, mass balance, dose proportionality, pharmacokinetic and pharmacodynamic dose titration, effect of food, pharmacokinetics in the elderly, pharmacokinetics in poor and extensive metabolizers of cytochrome P-450 2D6, effect of hepatic cirrhosis and a bioequivalence study to support a manufacturing site change. Additionally, drug interaction studies were conducted to assess the effects of fluoxetine, warfarin and ketoconazole on the pharmacokinetics of tolterodine and the effects of tolterodine on the pharmacokinetics and pharmacodynamics of warfarin, oral contraceptive containing ethinyl estradiol and levonorgestrel and probe drugs for cytochrome P-450s 2D6, 2C19, 3A4 and 1A2.

The overall conclusions derived from these studies are as follows;

Clinical

- Dry mouth was detected at 3.2 mg. Blood pressure was not affected at 6 mg, heart rate increased markedly after 6.4 mg, residual urine increased after 6.4 mg and near point of vision was increased after 12.8 mg.
- ECG has been extensively documented in several Clinical Pharmacology/pharmacokinetic studies. Special consideration has been taken to include those subjects in the analyses where the safety issue may be of special concern (elderly and poor metabolizers). No clinically significant changes are found in these groups.

Metabolism

- The major route of elimination is mediated by CYP2D6. A small proportion of the patients (7% of Caucasians, 1% Blacks and 1% Asians) to be treated will be poor metabolizers devoid of CYP2D6. In these subjects higher concentrations of tolterodine but not quantifiable concentrations of the primary metabolite, DD 01 will be present. The only metabolite found in serum in such subjects is dealkylated tolterodine formed via CYP3A isoenzymes which is not likely to contribute to the clinical effect.

- Accounting for the higher degree of protein binding of tolterodine compared with DD 01, and considering the antimuscarinic equipotency of the two moieties, there is strong evidence to support that it is DD 01 that accounts for the major part of the clinical effect in extensive metabolizers, while it is tolterodine in poor metabolizers. The same dosage regimen can be applied irrespective of phenotype.

Protein Binding

- Tolterodine and DD 01 are bound to α_1-acid glycoprotein. The protein binding of tolterodine in serum is relatively high while DD 01 has a low binding.

Pharmacokinetics

- Food does not result in clinically relevant changes in the kinetic profile.

- Single-dose kinetics of tolterodine and DD 01 have been proven to be linear covering clinically relevant doses. In addition, linearity is seen at higher doses up to 12.8 mg. Also in poor metabolizers dose proportionality is evident.

- Multiple-dose kinetics can be predicted from single-dose data and are consistent in phase I, II and III studies. There is no time dependent kinetics.

Special Populations

- The pharmacokinetics of tolterodine is similar in males and females.

- Differences in kinetic profile between races seems to be less than the difference between extensive and poor metabolizers, which has been thoroughly documented with respect to safety/tolerability.

- Fit elderly and young subjects show similar exposure to tolterodine and DD 01. Elderly on concomitant medication show a trend with higher exposure with increasing age which, however, is not reflected in increased frequency of dry mouth reporting. In the elderly poor metabolizers no change with age in exposure to tolterodine is found.

- After single 2 mg B.I.D. doses of Detrol, hepatic impairment results in higher serum concentrations of tolterodine compared to those in healthy subjects.

- Renal impairment has not been specifically studied. It is not expected that tolterodine and DD 01 will accumulate with reduced renal function. However, it is possible that tolterodine acid and its corresponding dealkylated metabolite may show changed kinetics.

Drug Interactions

- Interactions with other drugs are likely to have metabolic origin. Fluoxetine interacts by inhibition of CYP2D6 leading to increase in tolterodine average serum concentrations. The combined exposure to unbound tolterodine and DD 01 is only slightly higher than the exposure to unbound tolterodine in poor metabolizers.

- Tolterodine does not interact with warfarin as evidenced by prothrombin-time, factor VII response and warfarin pharmacokinetic profile.

- Tolterodine does not interact with oral contraceptives (levonorgestrel/ethinyl estradiol) as evidenced by monitoring of estradiol and progesterone.

II. Recommendation

The submission to NDA 20-771, submitted on March 2, 1997 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII). It is the opinion of OCPB/DPEII that the sponsor has provided appropriate clinical pharmacology and biopharmaceutics information to support the approval of Detrol™ (tolterodine L-tartrate) for the treatment of overactive bladder provided that Comments 1, 2, 3 and 4 (below) are met;

1. The sponsor submits the full study report for Study 97-OATA-036, including raw data and proper assay validation (inter- and intra-day precision and accuracy) for review.

2. The sponsor edits the product label according to the recommendations made in this review.

3. The proposed *in vitro* dissolution test method is acceptable. However, it is recommended that the drug release specifications be changed to Q= % at minutes.

4. The sponsor conduct a multiple dose pharmacokinetic and pharmacodynamic study in patients with hepatic impairment (cirrhosis) to assess the potential for ECG changes (prolongation of QTc interval). This study may be conducted Phase IV. The sponsor should propose a study design, including number of subjects, duration of treatment and time of ECG assessments and submit to the agency for review prior to the initiation of the study. This study should be completed within one year of the approval of this application.

5. The bioequivalence information provided to support the manufacturing site change from the Pharmacia AB plant in Malmo, Sweden to the Pharmacia & Upjohn plant in Ascoli, Italy is appropriate and is acceptable .

/S/

K. Gary Barnette, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 2/26/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 3/12/98

H 1/3/16/98

Clinical Pharmacology and Biopharmaceutic Briefing: 3/11/98
Attendees: Rarick, Shames, Hirsch, Lesko, Metz, M.Chen, Hunt, Mehta, Pelsor, Huang, Dorantes, Barnette.

cc: NDA 20-771, HFD-580 (Shames, Dunson), HFD-870 (M.Chen 13B-17, Dorantes, Barnette), Drug File (CDR, Barbara Murphy).

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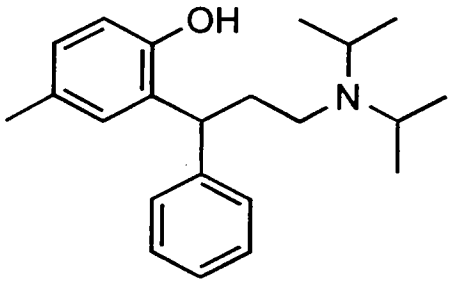
III. Background

Tolterodine L-tartrate is a synthetic muscarinic receptor antagonist. The chemical name of tolterodine is [R]-N,N-diisopropyl-3-(2-hydroxy-5-methyl-phenyl)-3-phenylpropanolamine. The chemical structure of the free base is shown below:



Normal bladder contractions are primarily initiated through cholinergic muscarinic receptor stimulation that may also play a major role in overactive bladder. The proposed clinical benefit of Detrol™ is that it exhibits selective antimuscarinic activity and the side effect profiles (dry mouth, etc.) may be lesser than those seen with current therapies (see Clinical review, Dr. Dan Shames, Medical Officer, Division of Reproductive and Urologic Drug Products).

Detrol™ is not marketed in any country worldwide. However, tolterodine was approved for marketing (Trade Name = Detrusitol®) in Sweden in September 1997.

Of significant safety concern is that compounds with similar chemical structure to tolterodine, i.e. terodiline (Bicor®, Mictrol, Micturin) have been associated with Torsades de Pointes and QTc prolongation. For this reason, terodiline is not currently marketed for the intended indication of angina pectoris (originally approved in Sweden, 1966).

IV. Formulation

The proposed to-be-marketed formulation is included in Table 1. It should be noted that the drug substance will be manufactured by

Table 1.

Component	1 mg Tablet	2 mg Tablet
TABLET CORE		
Tolterodine L-tartrate		
Cellulose, microcrystalline		
Calcium hydrogen phosphate dihydrate		
Sodium starch glycolate		
Magnesium stearate		
Colloidal anhydrous silica		
TABLET COATING		
	qs	qs

Reviewer Comment:

The proposed to-be-marketed formulation was used in all the Phase I, II and III clinical trials with the exception of increased quality of the sodium starch glycolate. However, a manufacturing site change between the clinically tested batches, manufactured at the Pharmacia AB plant in Malmo, Sweden to the proposed commercial batches to be manufactured at the Pharmacia & Upjohn plant in Ascoli Piceno, Italy has been proposed. An in vivo Bioequivalence study has been conducted and bioequivalence between the clinically tested batches and the proposed to-be-marketed batches has been established (see data in Bioequivalence section, Page 8).

V. *In Vitro* Dissolution Method and Validation

The proposed *in vitro* dissolution test method for tolterodine includes the following;

Apparatus	USP apparatus II (paddle)
Paddle Speed	50 rpm
Media	simulated gastric fluid (pH 1.2) without enzymes
Volume	900 ml
Specification	% dissolved in minutes (Q %)

The average and individual values (% dissolved) for the clinically tested 2 mg tablets and the proposed to-be-marketed 2 mg tablet using the aforementioned *in vitro* dissolution method are include in Table 2.

Table 2.

Time (min)	Avg±SD	1	2	3	4	5	6	7	8	9	10	11	12
Clinically Tested 2 mg Tablets													
	65±16.7	64	81	67	36	40	62	82	75	71	41	81	76
	91±6.6	94	95	84	81	89	91	99	91	92	82	102	97
	97±5.0	99	99	87	92	99	97	104	95	95	89	102	99
	98±3.7	**99**	**100**	**89**	**95**	**100**	**100**	**103**	**97**	**97**	**97**	**104**	**98**
Proposed To-Be-Marketed 2 mg Tablet													
	38±16.5	35	51	44	10	44	45	51	36	55	6	53	23
	85±6.4	81	93	85	79	89	87	85	85	87	70	93	81
	94±3.2	91	98	92	96	95	95	91	93	91	89	100	93
	96±2.5	**95**	**100**	**95**	**99**	**96**	**97**	**93**	**96**	**93**	**92**	**98**	**98**

Reviewer Comments:

1. *Detrol™ is an immediate release product.*

2. *The proposed in vitro dissolution test method is acceptable.*

3. *It is recommended that the proposed drug release specification be changed from % dissolved in minutes (Q = %) to % dissolved in minutes (Q %).*

VI. Analytical Methodology

Reviewer Comment:
The assay and validation of the assay used to estimate plasma, serum and urine tolterodine and DD01 levels are acceptable.

VII. Protein Binding

The degree of protein binding of tolterodine and DD01 at concentrations of μg/l was assessed by equilibrium dialysis. It was determined that both tolterodine and DD01 preferentially bind to α1-acid glycoprotein. The unbound fraction of tolterodine was 3.7 ± 0.13% and DD01 was 36 ± 4.0%. The affinity constants for tolterodine for α1-acid glycoprotein and albumin were 2.1×10^6 and 1.1×10^3 M^{-1}, respectively. While the affinity constants for DD01 for α1-acid glycoprotein and albumin were 1.3×10^5 M^{-1} and 4.5×10^2 M^{-1}, respectively.

Reviewer Comments:

DD01 is not as highly protein bound as tolterodine. Therefore, since tolterodine undergoes significant metabolism to form DD01 in extensive metabolizers, it is likely that the majority of the pharmacodynamic activity in extensive metabolizers can be attributed to DD01.

VIII. Pharmacokinetics

Table 5. Pharmacokinetic Study Summary

Protocol #	Objective	Dose (mg)	Dosing Regimen	Subjects	Pg #
90-023-00	Dose Titration	0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8	Single Dose	17 healthy	39
90-126-00	Mass Balance	5	Single Dose	6 healthy	42
91-007-00	Multiple Dose PK/Dose Selection	2, 4, 6	Multiple Dose	4 healthy	44
92-OATA-001	Single and Multiple Dose PK /Dose Selection	2, 4	Single & Multiple Dose	11 healthy	47
93-OATA-004	Polymorphism	4	Single & Multiple Dose	8 healthy	52
93-OATA-007	PK in Elderly	1, 2, 4	Single & Multiple Dose	26 healthy	53
93-OATA-013	PK in Elderly	1, 2	Single & Multiple Dose	33 elderly	57
94-OATA-022	Food Effect/Gender	2	Single Dose	23 healthy	60
95-OATA-024	Dose Proportionality/Gender	1, 2, 4	Single Dose	24 healthy	62
95-OATA-026	Hepatic Cirrhosis	2	Single Dose	16 healthy	64
95-OATA-028	Bioequivalence/Gender	2	Single Dose	24 healthy	68

A. Bioavailability

The absolute bioavailability of orally administered tolterodine was assessed in Study TRN 90-023-00 in 17 healthy male subjects 20-45 years of age.

The pharmacokinetic parameters generated from oral doses of solutions of mg of tolterodine and mg IV doses are included in Table 6.

Table 6. Mean (± SD) Pharmacokinetic Parameters

Dose	3.2 mg Oral Dose (n = 7)	6.4 mg Oral Dose (n = 8)	0.64 mg IV Dose (n=2)	1.28 mg IV Dose (n=8)
C_{max} (µg/l)	6.2 ± 4.6	9.6 ± 6.0	26	28 ± 12
T_{max} (h)	0.8 ± 0.2	0.9 ± 0.3	---	---
T½ (h)	2.7 ± 0.6	2.4 ± 0.69	3.3	2.7 ± 1.3
AUC (µg * h/l)	27.6 ± 22.5	36.6 ± 26.7	21.2	30.0 ± 7.95
CL_O (l/h)	120 ± 70.0	201 ± 143	20.7	30.5 ± 6.57
Vd (L)	---	---	131	113 ± 22.9
F (%)	39	29	---	---

Reviewer Comments:

1. *The oral dose of tolterodine used in Study 90-023-00 were aqueous solutions and not the proposed to-be-marketed formulation of Detrol™.*

2. *The doses studied herein are not the proposed to-be-marketed doses of 1 or 2 mg of tolterodine.*

3. *Although the bioavailability of tolterodine (F %) appears to be 30-40%, it should be noted that the primary metabolite that is created through first pass metabolism in extensive metabolizers, DD01, is equipotent to tolterodine and is likely to contribute the preponderance of the pharmacological activity in this population.*

B. Bioequivalence

The clinically tested formulations of tolterodine were manufactured at the Pharmacia AB plant in Malmo, Sweden, while the proposed manufacturing plant for the commercial product will be the Pharmacia & Upjohn plant in Ascoli, Italy. Additionally, a change in the quality of the sodium starch glycolate will also be made. Study CTN 95-OATA-028 is a single dose crossover study in 24 healthy volunteers conducted to assess the bioequivalence of tolterodine tablets from the two different production sites. The mean (± SD) pharmacokinetic parameters [except t_{max} which is given as median (range)] generated from this study are summarized in Table 7 and the statistical results for log transformed data are summarized in Table 8.

Table 7

	Tolterodine		DD 01	
Parameter	Ascoli	Malmö	Ascoli	Malmö
AUC(µg·h/l)	6.2 ± 3.4	6.0 ± 3.0	11.0 ± 2.8	11.2 ± 2.8
C_{max} (µg/l)	1.9 ± 1.1	1.9 ± 1.0	2.6 ± 1.0	2.6 ± 0.9
t_{max} (hours)	1.0 (0.5 - 3.0)	1.0 (0.5 - 1.5)	1.0 (0.5 - 1.5)	1.0 (0.5 - 2.0)
$t_{1/2z}$ (h^{-1})	2.3 ± 0.5	2.2 ± 0.3	2.8 ± 0.5	2.9 ± 0.5
CL/F (l/h)	287 ± 159	303 ± 197		

Table 8.

	AUC	C_{max}
Tolterodine	103 (94 - 114)	103 (91 - 118)
DD 01	98 (94 - 102)	98 (92 - 105)

Reviewer Comment:

Although Study 95-OATA-028 was an open label study, the results indicate that the tolterodine tablets manufactured at the Malmo, Sweden facility (clinically tested) and those manufactured at the Ascoli, Italy plant (proposed commercial manufacturer) are bioequivalent. However, it should be noted that according to SUPAC-IR a manufacturing site change such as the one outlined above could be supported using multi-point dissolution profile comparison (Case B).

C. Single Dose Pharmacokinetics

The single dose pharmacokinetics of the proposed to-be-marketed doses of tolterodine (1 or 2 mg) in normal healthy volunteers were assessed in Studies 92-OATA-001, 94-OATA-022, 95-OATA-024, 95-OATA-028. The mean (±SD) tolterodine pharmacokinetic parameters from these studies are summarized in Table 9.

Table 9.

Protocol #	n	2D6	tmax (h)	Cmax (µg/l)	AUC (µg*h/l)	t½ (h)
1 mg dose						
95-OATA-024	21 m/f 3 m/f	EM PM	1.0	1.1 ± 1.1	3.8 ± 3.3	2.5 ± 0.7
2 mg dose						
92-OATA-001	11 m	EM	2.0 ± 0.9	2.2 ± 2.1	12 ± 15	2.4 ± 0.7
94-OATA-022	22 m/f 1 f	EM PM	1.0 1.5	1.0 8.3	8.6 ± 10 93	2.3 ± 0.7 7.5
95-OATA-024	21 m/f 3 m/f	EM PM	1.0 1.5	2.1 ± 2.6 9.7 ± 2.7	7.5 ± 8.6 104 ± 22	2.6 ± 0.9 9.2 ± 0.9
95-OATA-028	24 m/f 24 m/f	EM EM	1.0 1.0	1.9 ± 1.1 1.9 ± 1.0	6.2 ± 3.4 6.0 ± 3.0	2.3 ± 0.5 2.2 ± 0.3

D. Multiple Dose Pharmacokinetics

The multiple dose pharmacokinetics of the proposed to-be-marketed dose of tolterodine (2 mg b.i.d.) in normal healthy volunteers were assessed in Studies 91-007-00, 92-OATA-001. The mean (±SD) tolterodine pharmacokinetic parameters from these studies are summarized in Table 10.

Table 10.

Protocol #	n	2D6	tmax (h)	Cmax (µg/l)	AUC (µg*h/l)	t½ (h)
2 mg dose						
91-007-00	4 m	?	0.9 ± 0.3	2.8 ± 1.1	13 ± 4.8	3.2 ± 0.6
92-OATA-001	11 m	EM	2.5 ± 1.1	2.5 ± 2.3	12 ± 14	2.4 ± 0.9

Reviewer Comment:

A between study comparison of the single and multiple dose pharmacokinetic data indicate consistent and comparable results.

E. Dose Proportionality

The dose proportionality of single doses over the proposed clinical dosing range (and above) was assessed in Study CTN 95-OATA-024. This study was an open, randomized, 3-period cross-over, single-dose study in 24 healthy volunteers (11 males, 13 females). The mean (± SD) pharmacokinetic parameters generated from this study are summarized in Tables 11.

Table 11. Mean (± SD) Pharmacokinetic Parameters (except t_{max} = median (range))

Parameter	2D6	1 mg		2 mg		4 mg	
		Tolterodine	DD 01	Tolterodine	DD 01	Tolterodine	DD 01
AUC_∞	EM	3.82±3.30	5.71±2.08	7.49±8.60	10.7±3.85	15.7±18.0	22.4± 8.94
(µg·h/l)	PM	55.7±2.83		104±22.3		231±23.5	
C_{max} (µg/l)	EM	1.1±1.1	1.2±0.46	2.1±2.6	2.2±0.75	4.6±6.0	4.8±1.7
	PM	4.7±1.2		9.7±2.7		18.8±5.1	
t_{max} (hours)	EM	1.0 (0.5-3.0)	1.0 (0.5-3.0)	1.0 (0.5-3.0)	1.0 (0.5-3.0)	1.0 (0.5-3.0)	1.0 (0.5-4.0)
	PM	1.5 (1.5-2.0)		1.5 (1.0-2.0)		1.5 (1.0-3.0)	
$t_{1/2z}$ (h^{-1})	EM	2.46±0.68	3.20±0.53	2.64±0.89	3.20±0.76	2.15±0.33	2.93±0.53
	PM	10.4±0.53		9.24±0.93		9.53±0.39	
CL_O (l/h)	EM	304±191		380 ±262		408±325	
	PM	12.3±0.61		13.5±2.65		11.9±1.16	

The statistical results of the dose normalized 1 and 4 mg doses, compared to the 2 mg dose (geometric mean with 90% CI) are summarized in Table 12.

Table 12.

	AUC_∞	C_{max}
Tolterodine		
1 mg	117 (103 - 132)	116 (99 - 137)
4 mg	102 (89 - 115)	105 (89 - 123)
DD 01		
1 mg	107 (99 - 115)	107 (96 - 120)
4 mg	104 (96 - 112)	106 (95 - 118)

Reviewer Comment:

Tolterodine exhibits proportional pharmacokinetics between doses of 1, 2 and 4 mg.

F. Food Effect

The influence of food on the bioavailability of tolterodine was assessed in an open, single dose cross over study in 24 healthy volunteers (Study 95-OATA-022). The pharmacokinetic parameters (mean ± SD; median with range for t_{max}) for tolterodine and DD 01 after oral administration of tolterodine with and without food are included in Table 13.

Table 13.

Parameter	Tolterodine		DD 01	
	Food	Fasting	Food	Fasting
C_{max} (µg/l)	2.7 ± 1.8	1.9 ± 1.4	2.1 ± 0.65	2.3 ± 0.89
AUC_{∞} (µg·h/l)	11.6 ± 11.7	8.63 ± 10.0	11.0 ± 2.76	10.2 ± 3.10
t_{max} (h)	1.0 (0.5 - 3.0)	1.0 (0.5 - 4.0)	1.0 (0.5 - 3.0)	1.0 (0.5 - 2.0)
$t_{½z}$ (h)	2.3 ± 0.54	2.3 ± 0.73	3.2 ± 0.99	3.2 ± 0.96
Cl_0 (l/h)	209 ± 148	376 ± 382		

Table 14. AUC_{∞} and C_{max} ratios (geometric mean with 90 % CI) for tolterodine and DD 01: Fed/Fast

	AUC_{∞} ratio	C_{max} ratio
Tolterodine	1.53 (1.35 - 1.72)	1.49 (1.30 -1.71)
DD 01	1.09 (1.04 - 1.15)	0.96 (0.87 - 1.06)

Reviewer's Comments:

1. *An ≈53% increase in extent of tolterodine absorption (AUC_{∞}) was seen when the drug was given with food.*

2. *Food had NO effect on the bioavailability of the active metabolite DD 01.*

3. *Although there is an ≈50% increase in tolterodine bioavailability when Detrol™ is given with food, due to the safety profile of tolterodine at doses of at least 4 mg b.i.d., the linear pharmacokinetics that exist over a dosing range of 1-4 mg and the lack of food effect on the bioavailability of DD01, there are no clinically significant safety concerns in extensive metabolizers and dose adjustment is not needed.*

4. *The effect of food on the bioavailability of tolterodine in poor metabolizers (individuals genetically deficient in CYP 2D6) has not been assessed.*

G. Special Populations

Hepatic Insufficiency

The effect of hepatic impairment on the pharmacokinetics of tolterodine was assessed in Study CTN 95-OATA-026. This was an open-label, single dose study in 16 patients with hepatic cirrhosis as determined by Child Pugh (classification A or B) or proven by liver biopsy (preferred), or liver-spleen scan (^{99m}Tc-sulfur colloid). The mean (± SD) pharmacokinetic parameters stratified into extensive and poor metabolizers (see Metabolism section, Page 12) generated from this study and a between study comparison of 2 mg single dose kinetic estimates from previous studies in normal elderly and healthy volunteers (extensive metabolizers) are included in Tables 15 and 16.

Table 15. Mean (± SD) Kinetic Parameters of Tolterodine in Extensive Metabolizers (EM) and Poor Metabolizers (PM)

	Normal Healthy Volunteers		Cirrhotic Patients	
	EM (n=21)	PM (n=8)	EM (n=14)	PM (n=2)
Age: range (yr.)	21-42	19-47	42-68	42-68
C_{max} (ng/mL)	2.11 (2.6)	10.0 (4.9)	5.7 (3.4)	range: 6.4 - 10.2
$AUC_{0-\infty}$ (ng·hr/mL)	7.49 (8.60)	100 (51)	57.7 (59.4)	range: 124 - 199
CL_O (L/hr/kg)	5.65 (3.84)		1.0 (1.7)	0.09-0.16
$t_{½z}$ (hr)	2.63 (0.89)	6.5 (1.6)	7.8 (4.7)	range: 13.5 - 15.7

Table 16. Mean (± SD) Kinetic Parameters of DD 01 in Extensive Metabolizers

	Normal Healthy Volunteers (n = 21)	Cirrhotic Patients (n = 14)
Age: range (y)		
C_{max} (ng/mL)	2.2 (0.75)	1.4 (0.85)
$AUC_{0-\infty}$ (ng·hr/mL)	10.7 (3.85)	14.8 (7.32)
$t_{½z}$ (hr)	3.20 (0.76)	9.8 (7.2)

Reviewer's Comments:

1. *The bioavailability of tolterodine is significantly increased and the clearance of tolterodine is significantly decreased in hepatic impaired patients.*

2. *The proposed dosing regimen is 2 mg b.i.d. and may reduced to 1 mg b.i.d. if significant side effects occur. The sponsor is recommending that the dosing regimen in patients with hepatic impairment be no greater than 1 mg b.i.d. This recommendation is acceptable.*

3. *In multiple dose studies in dogs, resulting in tolterodine blood levels >600 µg/ml and DD01 levels of >100 µg/ml, a 10-20% increase in the QT interval occurs after 9 days of tolterodine treatment. Therefore, the sponsor should conduct a multiple dose PK/PD study in patients with hepatic impairment to assess the ECG changes at steady state.*

Renal Insufficiency

No studies have been conducted in renally impaired patients and no dose adjustment is recommended in this special population.

Reviewer Comment:

Since tolterodine and the primary active metabolites are eliminated primarily through hepatic metabolism and this product has a relatively wide therapeutic window, a study in renally impaired patients would not likely result in any clinically significant information. Therefore, I concur with the sponsor's assessment that no dose adjustment be recommended in renally impaired patients.

Gender

Analysis of gender differences in the pharmacokinetics of 2 mg doses of tolterodine was assessed in three single dose studies, 94-OATA-022, 95-OATA-024, 95-OATA-028 in fasting healthy volunteers. Table 17 summarizes the pharmacokinetic data from all three studies, by gender.

Table 17. Mean[1] (± SD) pharmacokinetic parameters in all three studies, by sex.

Parameter	Tolterodine			DD 01		
	Females (n = 37)	Males (n = 30)	p-value	Females (n = 37)	Males (n = 30)	p-value
AUC (µg·h/l)	7.8 ± 7.4	6.7 ± 8.0	0.54	11 ± 3.2	10 ± 3.2	0.47
C_{max} (µg/l)	2.2 ± 2.1	1.6 ± 1.3	0.17	2.5 ± 0.94	2.2 ± 0.74	0.22
t_{max} (h)	1.0 (0.5 - 3.0)	1.0 (0.5 - 4.0)	0.41	1.0 (0.5 - 3.0)	1.0 (0.5 - 1.5)	0.61
$t_{½}$ (h)	2.4 ± 0.7	2.4 ± 0.6	0.30	3.0 ± 0.7	3.3 ± 0.8	0.078
CL_O (l/h)	310 ± 216	402 ± 352	0.20	n.a.	n.a.	n.a.

[1] = Median and range for t_{max} n.a. = Not applicable

Reviewer Comment:
There is no significance gender effect in the pharmacokinetics of tolterodine.

Age
The pharmacokinetic parameters of tolterodine, 1 and 2 mg b.i.d. in 10 healthy elderly volunteers (aged 70 years or older) with CYP2D6 (extensive metabolizers) were assessed in Study 93-OATA-013. The mean (± SD) tolterodine pharmacokinetic parameters in extensive metabolizers are included in Table 18.

Table 18.

Study	Age (yrs)	N	Dose	tmax (h)	Cmax(µg/l)	AUC (µg·h/l)	t½ (h)
93-OATA-013	>70	26	1 mg	1.0 ± 0.4	2.4 ± 1.6	8.6 ± 4.9	2.1 ± 0.6
			2 mg	0.9 ± 0.5	4.1 ± 3.8	14.0 ± 9.4	2.2 ± 0.7
91-007-00	64-80	33	2 mg	0.9 ± 0.3	2.8 ± 1.1	13 ± 4.8	3.2 ± 0.6
92-OATA-001	18-40	36	2 mg	2.5 ± 1.1	2.5 ± 2.3	12 ± 14	2.4 ± 0.9

Reviewer Comment:
A between study comparative assessment of an age related effect on the pharmacokinetics of 2 mg b.i.d. doses of tolterodine (elderly versus non-elderly volunteers) indicates that there is no significant difference between elderly and non-elderly subjects in extent of absorption (AUC). However, there did appear to be a difference in rate of absorption (Tmax). The clinical significance of this difference is likely to be limited.

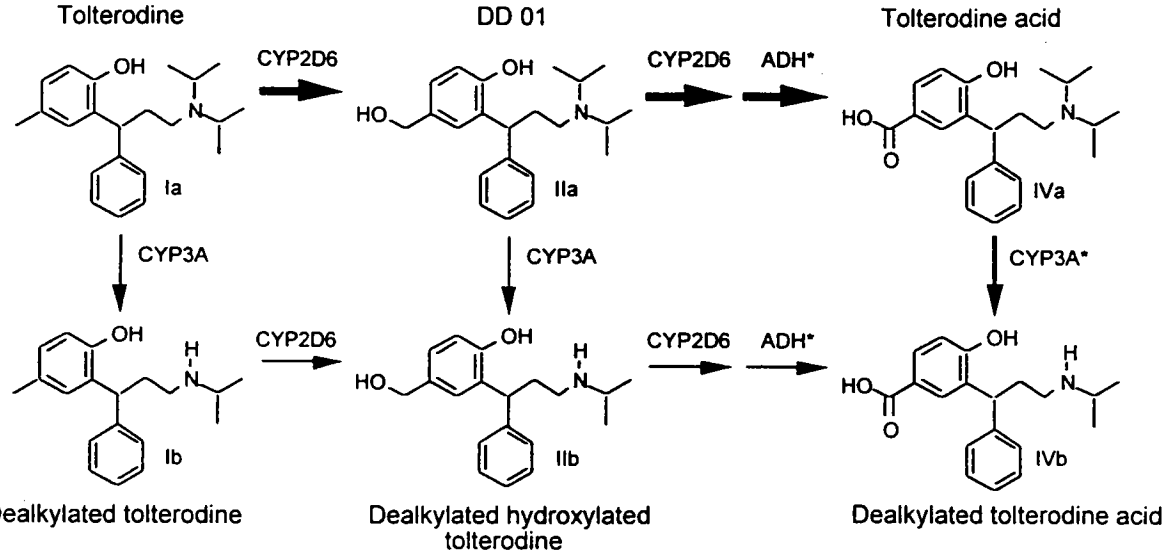
IX. Metabolism

Table 19. Metabolism Study Summaries

In Vivo Drug Interaction Studies					
Study #	Co-administered Compound(s)	Dose (mg)	Dosing Regimen	Subjects	Pg#
95-OATA-020	Marker Substrates	2	Single Dose	12 healthy	69
95-OATA-030	Fluoxetine	2	Multiple Dose	9 healthy	71
95-OATA-025	Warfarin	2	Multiple Dose	20 healthy	73
95-OATA-027	Oral Contraceptive	2	Multiple Dose	24 healthy	77
In Vitro Drug Metabolism Studies					
Study #	Tissue	Objective			
9500401	Human Liver Microsomes	Correlation with marker substrate turnover			
9500404	Human Liver Microsomes	Incubations with known 2D6 and 3A4 inhibitors			
9500402	β-lymphoblastoid Cells	Formation rate of DD01 and Dealkylated tolterodine			
9500403	β-lymphoblastoid Cells	DD01 metabolism			
9600515	β-lymphoblastoid Cells	Dealkylated tolterodine metabolism			
9600546	β-lymphoblastoid Cells	Tolterodine Vmax and Km determination			

Tolterodine is primarily eliminated by hepatic metabolism. The proposed metabolic pathway for tolterodine is included in Figure 1. The rationale and justification for this pathway are included following the figure.

Figure 1.



A. Mass Balance

The disposition of a single 5 mg oral solution of [^{14}C]-labeled tolterodine administered to 6 healthy male volunteers was assessed in Study 90-126-00. The total recovery of radioactivity is given in Table 20.

Table 20. Total excretion of radioactivity in 7 days

	Subject Number						
	1	2	3	4	5	6	Mean ± S.D.
Urine (%)	79	71	74	79	81	80	77 ± 4.0
Feces (%)	15	24	15	15	16	17	17 ± 3.5
Total (%)	94	95	90	95	97	96	94 ± 2.5

Reviewer Comment:

The metabolites of tolterodine are primarily eliminated in the urine and is almost completely eliminated 7 days after a single oral solution dose.

B. In Vitro Drug Metabolism

To characterize the full metabolic profile of tolterodine the sponsor conducted *in vitro* drug metabolism studies. These studies included incubating [^{14}C]-labeled tolterodine and metabolites with human liver microsomes or human B-lymphoblastoid cell lines containing either CYP2D6 or CYP3A4. The abbreviated summaries of these studies are as follows;

Report 9500401

Characterization of the human cytochrome P450 isoenzymes involved in the *in vitro* metabolism of [^{14}C]-tolterodine in 10 human livers.

Substrate Concentration = 154 μM tolterodine
Tissue = 1 mg human liver microsomal protein

Results: The rate formation of DD01, dealkylated hydroxylated tolterodine and dealkylated tolterodine were correlated with marker substrate metabolism rates. The R^2 values of the aforementioned correlations are indicated in Table 21.

Table 21.

Substrate	CYP	DD01	N-dealkylated hydroxylated tolterodine	N-dealkylated tolterodine
7-ethoxyresorufin o-deethylation	1A	0.13	0.01	7E-3
caffeine 3-demethylation	1A	0.19	0.05	0.03
coumarin 7-hydroxylation	2A	5E-3	0.33	0.13
tolbutamide methyl-hydroxylation	2C	0.15	0.15	0.64
s-mephenytoin 4-hydroxylation	2C	0.19	0.03	0.03
dextromethorphan O-demethylation	2D	**0.87**	0.05	0.14
chlorzoxazone 6-hydroxylation	2E	0.03	2E-3	0.22
testosterone 6b-hydroxylation	3A	0.01	**0.68**	**0.97**
lauric acid 12-hydroxylation	4A	0.12	0.21	0.43

Report 9500404

Effect of cytochrome P450 inhibitors on the metabolism of [^{14}C]-tolterodine in human liver microsomes.

Substrate Concentration = 50 μM tolterodine

Tissue = 1 mg human liver microsomal protein

Results: The IC50 of inhibitors of CYP 3A4 and CYP 2D6 were assessed in pooled human liver microsomes. The IC50s are included in Table 22.

Table 22.

Inhibitor	CYP	DD01	N-dealkylated tolterodine
quinidine	2D6	<200 μM	<400 μM
troleadomycin	3A4	<50 μM	<1 μM
ketoconazole	3A4	----	<1μM

Report 9500402

Metabolism of [^{14}C]-tolterodine by human B-lymphoblastoid cell lines expressing CYP 2D6 or CYP 3A4.

Substrate concentration = 154 μM tolterodine

Tissue = 2 mg B-lymphoblastoid cell microsomes

Results: The rate of formation of DD01 and dealkylated tolterodine were assessed and are reported in Table 23.

Table 23. Rate of formation (pmol/ nmol CYP450/min)

	CYP 2D6	CYP 3A4
DD01	1.400 ± 4.7	----
Dealkylated tolterodine	----	650 ± 36

Report 9500403

Metabolism of [^{14}C]-DD01 by human B-lymphoblastoid cell lines expressing CYP 2D6 or CYP 3A4.

Substrate Concentration = 50 μM DD01

Tissue = 2 mg B-lymphoblast cell microsomes

Results: The rate of formation of dealkylated hydroxylated tolterodine and tolterodine acid were assessed and are reported in Table 24.

Table 24. Rate of Formation (pmol/nmol CYP450/min)

	CYP 2D6	CYP 3A4
Dealkylated hydroxylated tolterodine	26 ± 0	495 ± 31
Tolterodine Acid	644 ± 32	126 ± 69

Report 9600515

Metabolism of N-dealkylated tolterodine by recombinant CYP 2D6.

Substrate Concentration = 176 μM N-dealkylated tolterodine.

Tissue = 2 mg B-lymphoblast cell microsomes

Results: The rate of formation of N-dealkylated hydroxylated tolterodine and N-dealkylated tolterodine acid were assessed and are reported in Table 25.

Table 25. Rate of Formation (pmol/nmol CYP450/min)

N-dealkylated hydroxylated tolterodine	3434 ± 48
N-dealkylated tolterodine acid	2862 ± 332

Report 9600546

Kinetic studies of [^{14}C]-tolterodine by recombinant human CYP 2D6 and CYP 3A4.

Substrate Concentrations:12.5, 25, 50, 75, 100, 150, 200 and 400 μM tolterodine.

Tissue = 0.5 mg B-lymphoblast cell microsomes

Results: The Vmax and Km for the formation of DD01 (catalyzed primarily by CYP 2D6) and N-dealkylated tolterodine (catalyzed primarily by CYP 3A4) were estimate by Lineweaver-Burke (1/V versus 1/S) and by Eadie-Hofstee (V/S versus V). The estimates are included in Table 26.

Table 26.

Metabolite	DD01	N-dealkylated tolterodine
Lineweaver-Burke Plot		
Vmax (pmol/nmol P450/min)	11779	1326
Km (μM)	31	29
Eadie-Hofstee Plot		
Vmax (pmol/nmol P450/min)	12128	1366
Km (μM)	33	37

Reviewer Comments:

1. *The Cmax for 2 mg b.i.d. dosing regimen of tolterodine is 2-3 μg/l (0.004 - 0.006 μM). Therefore, the tolterodine concentration (154 μM) used in most of these in vitro drug metabolism studies is over 30,000 times higher than the observed Cmax concentration from the proposed to-be-marketed dose.*

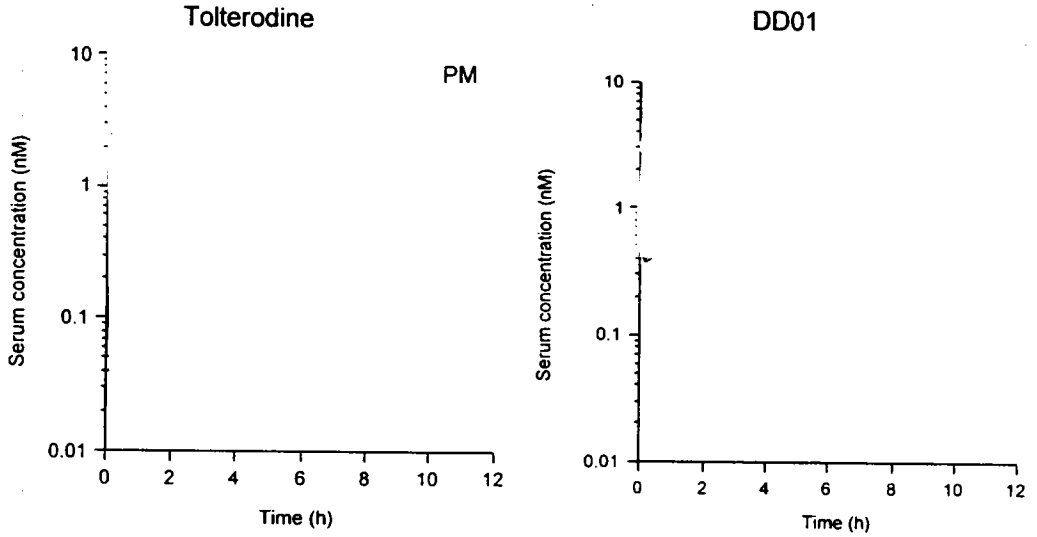
2. *Based on the data from the in vitro drug metabolism studies using a relatively high concentration of tolterodine, I concur with the sponsor's proposed metabolic pathways for tolterodine (see Figure 1, above).*

3. *It appears that the Vmax for the formation of DD01 (CYP2D6) is approximately 10 fold higher than that for the formation of N-dealkylated tolterodine (CYP3A4), thus indicating a higher turnover rate for CYP2D6 and confirming the assumption that in extensive metabolizers, the primary route of tolterodine elimination is metabolism by CYP 2D6 to form DD01.*

C. In Vivo Drug Metabolism

As was previously stated, tolterodine is primarily eliminated via hepatic metabolism and the primary metabolic routes of elimination are through the catalytic activity of cytochrome P-450 2D6 and 3A4. Cytochrome P-450 2D6 is a genetically polymorphic enzyme that is absent in approximately 7% of Caucasians, 1% East Asians and 1% Black Americans. Due to the lack of CYP2D6, the hydroxylated metabolite, DD01 will not be formed in these patients and the serum concentrations of intact tolterodine at steady state with a bid dosage regimen will be higher. Accounting for the differences in serum protein binding of DD 01 and tolterodine (Figure 2), and considering the *in vitro* antimuscarinic equipotency of the tolterodine and DD01, it appears that the efficacy of Detrol™ in extensive metabolizers is primarily due to DD 01, while it is tolterodine in poor metabolizers.

Figure 2. Unbound serum concentration-time profiles of tolterodine (left) and DD 01 (right) after 4 mg bid in extensive metabolizers and poor metabolizers.



The pharmacokinetic parameters for other relevant metabolites of tolterodine (see Figure 1) from Studies 95-OATA-024 (single dose) and 95-OATA-030 (multiple dose) are included in Table 27.

Table 27. Pharmacokinetic parameters of metabolites other than DD 01 after single-dose administration of tolterodine 4 mg (95-OATA-024) or multiple-dose administration of tolterodine 2 mg bid (95-OATA-030).

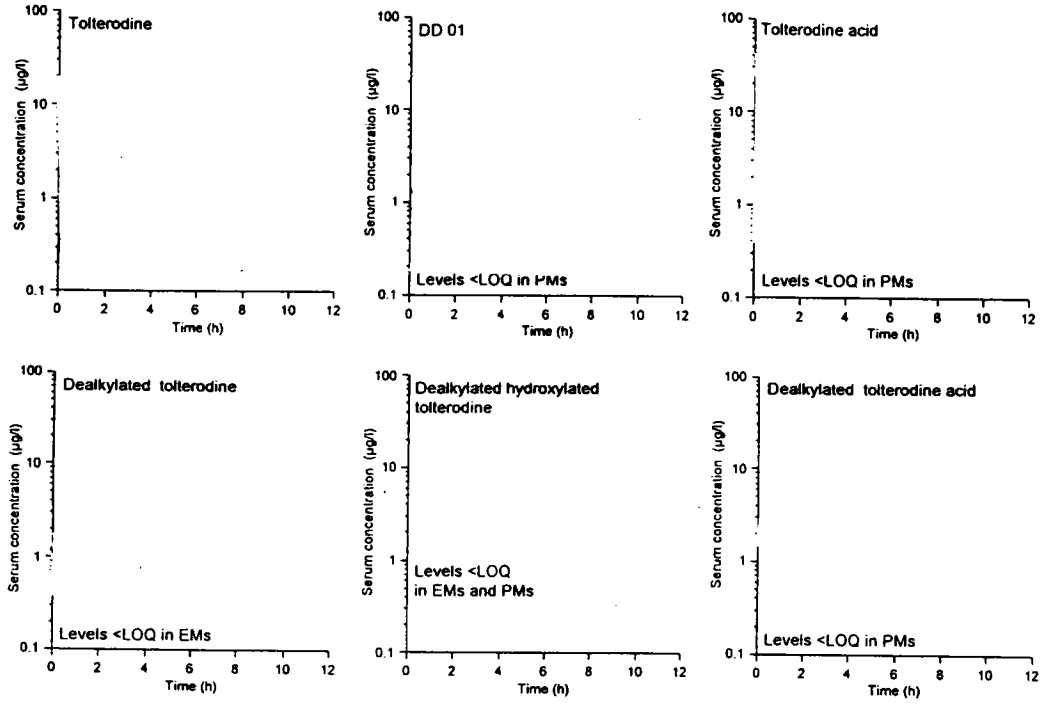
Metabolite	2D6	Dose (mg)	tmax (h)	Cmax (µg/l)	AUC (µg h/l)	$t_{1/2}$ (h)	Study #
Dealkylated tolterodine	EM	4	-	-	-	-	95-OATA-024
	PM	4	4.0	1.0	32	a	
	EM	2 bid	-	-	-	-	95-OATA-030
	PM	2 bid	7.0	1.1	12	a	
Dealkylated hydroxylated tolterodine	EM	4	-	-	-	-	95-OATA-024
	PM	4	-	-	-	-	
	EM	2 bid	-	-	-	-	95-OATA-030
	PM	2 bid	-	-	-	-	
Tolterodine acid	EM	4	2.0	20	121	3.3	95-OATA-024
	PM	4	-	-	-	-	
	EM	2 bid	1.9	9.7	61	6.7	95-OATA-030
	PM	2 bid	-	-	-	-	
Dealkylated tolterodine acid	EM	4	3.0	7.2	49	4.4	95-OATA-024
	PM	4	-	-	-	-	
	EM	2 bid	2.0	6.6	47	5.4	95-OATA-030
	PM	2 bid	-	-	-	-	

- serum concentrations < LOQ [a]Not enough data to estimate half-life

The primary metabolite of tolterodine in poor metabolizers is dealkylated tolterodine (catalyzed by CYP3A4). The dealkylated tolterodine to tolterodine peak serum concentration ratio is 1.0/18.8. Dealkylated tolterodine is ≈86% bound to α1-acid glycoprotein (tolterodine is ≈97% bound) and the antimuscarinic potency relative to tolterodine is about 1/20 (data not shown). The contribution of dealkylated tolterodine in the pharmacological effect of Detrol™ is approximately 1% in poor metabolizers.

The multiple dose (b.i.d.) plasma concentration versus time profiles of tolterodine, DD01 and the other metabolites from Study 95-OATA-030 are included in Figure 3. It should be noted that the profiles from the poor metabolizers (n=2) include symbols (•), while those from extensive metabolizers do not contain symbols.

Figure 3. Serum-concentration time profiles of tolterodine and its metabolites after oral multiple-dose administration of tolterodine 2 mg b.i.d.



Reviewer Comments:

1. *In extensive metabolizers, tolterodine acid and dealkylated hydroxylated tolterodine are present. In poor metabolizers, however, only dealkylated tolterodine was found. These findings are consistent with the metabolic pathways identified in the in vitro drug metabolism testing and indicate that CYP2D6 catalyzes the formation of tolterodine acid and dealkylated hydroxylated tolterodine, in addition to catalyzing the formation of DD01.*

2. *From Study 95-OATA-030, it appears that no accumulation of tolterodine acid or its dealkylated metabolite was seen in extensive metabolizers, and no accumulation of dealkylated tolterodine in poor metabolizers occurs after multiple dosing of 2 mg b.i.d.*

3. *The plasma dealkylated tolterodine concentrations observed in poor metabolizers, along with protein binding and in vitro activity data, indicate that this metabolites does not contribute a significant amount to the efficacy of Detrol™.*

X. Drug Interactions

Due the significance of metabolism in the elimination of tolterodine, metabolic based drug interaction studies to assess the affect of fluoxetine (CYP2D6) and warfarin on tolterodine pharmacokinetics were conducted. Additionally, the affects of tolterodine on the pharmacokinetics of warfarin, Neovletta® (ethinyl estradiol/levonorgestrel) oral contraceptive, and on marker substrates (probe drugs) for CYP2D6, CYP2C19, CYP3A4 and CYP1A2 were also assessed. After inquiries by this reviewer concerning the safety of coadministration of Detrol™ and a CYP3A4 inhibitor (i.e. ketoconazole) in poor metabolizers and possible accumulation of tolterodine, the sponsor submitted the summary results of Study 97-OATA-036 " Influence of ketoconazole on the pharmacokinetics and safety of tolterodine. An open, single group study in healthy volunteers." The results of these studies are included below.

Study 95-OATA-030: *Fluoxetine effect on Detrol™ Pharmacokinetics*

Table 28. Pharmacokinetic parameters of tolterodine and its metabolites after 2 mg (b.i.d.) administration of tolterodine tartrate for 2.5 days and coadministered with fluoxetine (mean±S.D.) in EMs.

Metabolite	Tolterodine (Day 3)				Tolterodine + Fluoxetine (Day 27			
	t_{max} (h)	C_{max} (µg/l)	AUC_τ (µg h/l)	$t_{1/2z}$ (h)	t_{max} (h)	C_{max} (µg/l)	AUC_τ (µg h/l)	$t_{1/2z}$ (h)
Tolterodine	0.8±0.2	3.6±2.6	17±20	3.7±2.1	1.2±0.3	13±4.8	81±30	5.7±1.7
DD 01	0.9±0.3	2.9±1.3	14±6.4	4.9±3.7	1.1±0.3	1.4±0.57	11±4.2	10±3.2
Tolterodine acid	1.9±0.2	9.7±5.2	61±27	6.7±7.6	2.3±1.7	2.4±1.2	22±11	19±18
Dealkylated tolterodine acid	2.0±0.0	6.6±1.3	47±6.3	5.4±1.1	1.3±0.7	1.8±0.70	18±6.2	38±22

Study Conclusions:
Fluoxetine significantly impaired the metabolism of tolterodine and an 4.8 fold increase of the AUC was seen in extensive metabolizers. Fluoxetine is primarily metabolized by CYP2D6. Therefore, in extensive metabolizers, competitive inhibition of the metabolism of tolterodine to DD01 is likely and indeed, this was observed.

The rate of formation of DD01 (Cmax) was significantly altered, but the extent of exposure (AUC) of DD01 was relatively unchanged in extensive metabolizers receiving fluoxetine. However, since CYP2D6 also catalyzes the metabolism of DD01 to tolterodine acid and this reaction would also be inhibited by fluoxetine, this observation is not unexpected.

Although relatively weak, fluoxetine has been shown to have CYP3A4 inhibitory capabilities. Therefore, the 24% increase in AUC in poor metabolizers may be due to the inhibition of the formation of dealkylated tolterodine, mediated by CYP3A4.

Study 95-OATA-025: *Tolterodine effect on Warfarin Pharmacokinetics and Pharmacodynamics and effect of Warfarin on Tolterodine Pharmacokinetics.*

Study Conclusions:
No pharmacokinetic or pharmacodynamic interaction was observed between warfarin and tolterodine.

Study 95-OATA-027: *Tolterodine effects on Oral Contraceptive Pharmacokinetics.*

Study Conclusions:
Coadministration of tolterodine with Neovletta®, an oral contraceptive containing ethinyl estradiol and levonorgestrel did not result in any clinically significant changes in ethinyl estradiol or levonorgestrel pharmacokinetics.

Study 95-OATA-020: *Tolterodine effect on the Pharmacokinetics of Probe Drugs for Cytochrome P-450s 2D6, 2C19, 3A4 and 1A2.*

Table 29. Mean metabolic ratios for the three probe drugs in 8 extensive metabolizers and 4 poor metabolizers of CYP2D6 Before, During and After Coadministration of Detrol™.

		Extensive Metabolizers / Poor Metabolizers		
Probe drug	Enzyme	Before	During	After
Debrisoquine	CYP2D6	0.49 / -	0.50 / -	0.46 / -
Omeprazole	CYP2C19	2.4 / 1.6	2.2 / 2.6	2.1 / 1.6
Omeprazole	CYP3A4	1.8 / 1.2	1.5 / 1.7	1.6 / 1.4
Caffeine	CYP1A2	6.2 / 4.5	7.0 / 4.2	6.3 / 3.9

Study Conclusions
The hydroxylation of debrisoquine (CYP2D6) was not affected by tolterodine. Inhibition of CYP2D6 is not likely. Inhibitors of CYP2D6 might, however, inhibit the metabolism of tolterodine.

The hydroxylation of omeprazole (CYP2C19) was not affected by tolterodine. Induction or inhibition of CYP2C19 is not likely.

Omeprazole sulphoxidation (CYP3A4) was not changed by tolterodine in neither extensive metabolizers nor poor metabolizers of CYP2D6 despite five to ten-fold higher concentration of tolterodine in poor metabolizers. The present data do not suggest metabolic interactions with CYP3A4 substrates.

N_3-demethylation of caffeine (CYP1A2) was not affected by tolterodine. Induction or inhibition of CYP1A2 is not likely.

Study 97-OATA-036: *Ketoconazole effects on Detrol™ Pharmacokinetics and Safety in Poor Metabolizers.*

Table 30.

Treatment	tmax (h)	Cmax (µg/l)	AUC0∞ (µg*h/l)	t½ (h)	CL/F (l/h)
Tolterodine	1.3±0.45	10±2.7	129±45	12±4.3	9.7±2.7
Tolterodine + Ketoconazole	1.8±1.5	20±9.8	332±135	15±5.4	4.7±1.8

Study Conclusions:
Tolterodine metabolism is significantly inhibited by ketoconazole in poor metabolizers of CYP2D6.

Cmax and AUC of tolterodine increased 2.0 and 2.7 fold, respectively, during coadministration of ketoconazole.

Reviewer Comments:
1. *Caution should be taken when co-administering CYP2D6 inhibitors (i.e. fluoxetine, quinidine, etc.) with Detrol™.*

2. *Combined tolterodine and warfarin dosing is deemed safe and well tolerated.*

3. *Based on pharmacokinetic data, tolterodine will not compromise oral contraceptive (ethinyl estradiol and levonorgestrel) efficacy and safety when coadministered.*

4. *Coadministration of tolterodine did not affect the pharmacokinetics of probe drugs for CYP2D6, CYP3A4, CYP2C19 and CYP1A2 and inhibition or induction of these enzymes by Detrol™ is unlikely.*

5. *The full study report for 97-OATA-036 has not been submitted to the FDA at this time. Therefore, upon submission and review of the full study, additional comments (labeling and otherwise) may be forthcoming.*

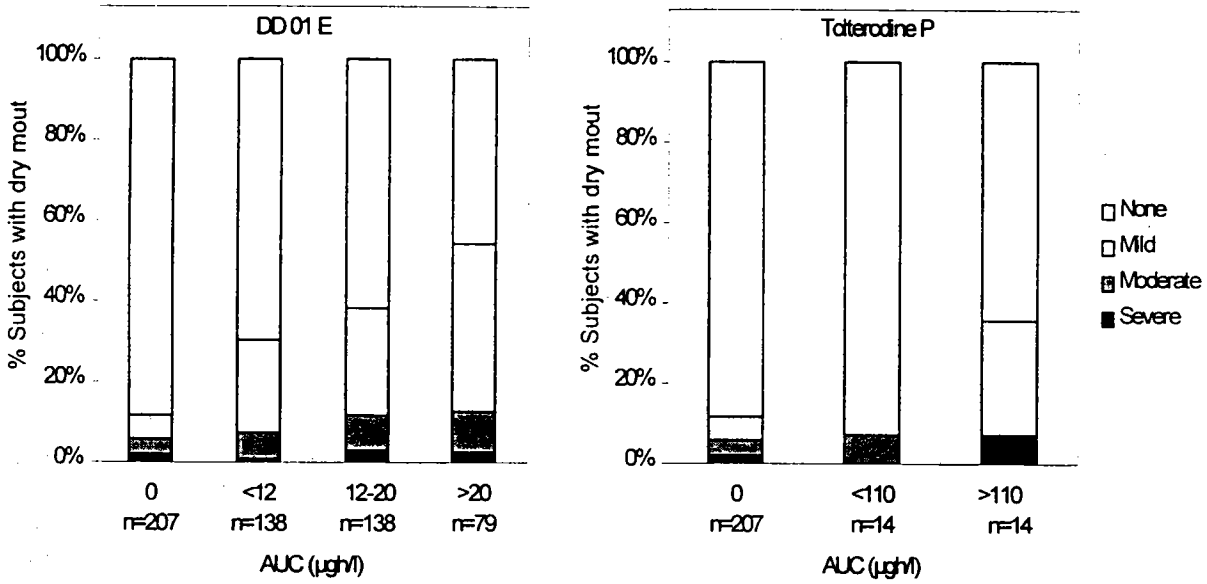
6. *Due to the potentially significant interaction between CYP3A4 inhibitors and Detrol™ in poor metabolizers, dosing of Detrol™ should be no greater than 1 mg b.i.d. when coadministered with CYP3A4 inhibitors. Similarly, since administration of a CYP2D6 inhibitor results in "poor metabolizer like" pharmacokinetics in extensive metabolizers, patients receiving a CYP2D6 inhibitor and a CYP3A4 inhibitor concurrently should also be dosed at rates no greater than 1 mg Detrol™ b.i.d.*

XI. Pharmacokinetic/Pharmacodynamic (Adverse Event) Relationship
The total incidence of dry mouth was 12% in placebo, 39% in extensive metabolizers and 21% in poor metabolizers and the incidence of moderate and severe intensity of dry mouth was 5.8% in placebo, 10%

in extensive metabolizers and 7.1% in poor metabolizers. The relationship between AUC (as estimated by sparse sampling) and dry mouth intensity was assessed in the Phase III clinical trials.

It was determined that an increased incidence of dry mouth is seen with increased systemic exposure, both for DD 01 in extensive metabolizers and for tolterodine in poor metabolizers. This is illustrated in Figures 4, below. Interestingly, at similar unbound AUCs in extensive metabolizers (sum of DD 01 and tolterodine: 13.8 nmol·h/l) and in poor metabolizers (tolterodine: 12.3 nmol·h/l), similar effect on dry mouth, 38% and 36%, respectively, is seen.

Figure 4. Relationship between AUC of DD 01 and dry mouth intensity in extensive metabolizers (right) and between the AUC of tolterodine and dry mouth in poor metabolizers (left).



Reviewer Comment:

There seems to be a relationship between drug exposure and the primary adverse event, dry mouth. This should provide patients and physicians a relatively non-serious adverse event to determine the proper dose an individual patient should receive. Therefore, the patient should be thoroughly counseled on dry mouth and the steps that should be taken if dry mouth occurs.

XII. Safety

Tolterodine is structurally similar to , which was withdrawn from marketing due to prolongation of the QTc interval. Hence, the potential hazards of tolterodine in light of the history of was assessed in the Phase II and III clinical trials.

Table 31. Mean (±SD) Change in QTc (ms) from baseline to day 14 in Phase II Studies.

Placebo (n=58)	0.5 mg b.i.d. (n=62)	1 mg b.i.d. (n=57)	2 mg b.i.d. (n=56)	4 mg b.i.d. (n=52)
2±18	6±9	2±18	10±17	7±17

Table 32. Mean (±SD) Change in QTc (ms) from baseline to Week 12 in patients on concomitant diuretic treatment.

Phase III Study 94-OATA-009		
Placebo (n=3)	1 mg bid (n=13)	2 mg bid (n=10)
11±24	-1±22	12±29

Table 33. Mean (±SD) Change in QTc (ms) from baseline to Week 4 in the potentially highest risk patients, the elderly.

Phase III Study 94-OATA-012		
Placebo (n=33)	1 mg bid (n=42)	2 mg bid (n=60)
- 2±14	7±16	2±18

The sponsor's conclusions from the safety analysis of the Phase II and III clinical trials indicate that tolterodine does not influence the QTc interval and no pathological morphology changes of the T-waves have been observed during tolterodine treatment. Additionally, concomitant medication with diuretics has no effect on the measured ECG variables and concomitant treatment with the anti-depressant drug fluoxetine, which alters the serum concentration of tolterodine and its pharmacologically active metabolite, does not influence ECG data. ECG data are similar in extensive and poor metabolizers of tolterodine.

It should be noted a modest increase in heart rate was noted at tolterodine doses of 2 and 4 mg bid. This increase was greater in women than in men.

Reviewer Comments

1. *The changes in QTc observed in association with tolterodine treatment at clinically relevant doses appear to be comparable to the changes in QTc observed in the placebo groups.*

2. *For further safety data analyses and their clinical significance, please see the Clinical Review, completed by Dr. Dan Shames, Medical Officer, Division of Reproductive and Urologic Drug Products.*

XIII. Labeling

The Clinical Pharmacology section of the label has been reviewed and the following changed are recommended. Text that is to be removed is stricken with a line. Additions are double underscored.

1. A Table should be added including the single and multiple dose pharmacokinetic parameters (i.e. Cmax, Tmax, Cave, clearance and t½) for tolterodine and DD01 in extensive and poor metabolizers.

2. The introductory text of the **CLINICAL PHARMACOLOGY** section should be edited as follows;

Redacted 16

pages of trade

secret and/or

confidential

commercial

information

XV. Attachment 2 (Study Summaries)

Study Number: TRN 90-023-00

Study Title: PHARMACOKINETICS AND TOLERABILITY OF TOLTERODINE AFTER ORAL AND INTRAVENOUS SINGLE-DOSE ADMINISTRATION TO HEALTHY VOLUNTEERS.

Study Objectives: The study had four main aims:
(i) To determine the oral threshold dose for pharmacological effects of tolterodine;
(ii) To get initial estimates of the kinetics of tolterodine up to the pharmacological threshold dose;
(iii) To study the oral kinetics of tolterodine at the pharmacological threshold dose and twice this dose;
(iv) To study the kinetics of tolterodine given intravenously at a dose corresponding to 1/10 - 1/5 of the oral pharmacological threshold dose;

Dosage and Administration: An aqueous solution of tolterodine for oral administration, was given as an infusion over 5 min (0.64 mg) and 10 min (1.28 mg), batch No. HrJ 237.

The choice of the first intravenous dose of tolterodine given to man was based on the chronotropic effect on the heart - the critical safety effect parameter. The lowest dose which gave significant deviation from the baseline was used to define the threshold dose. A 20% deviation of the mean value effect profile (deviation from basal value relative to mean value of all subjects at corresponding time points) at a dose level was the criterion for a significant observation. The initial intravenous dose should be 1/10 of the above defined threshold dose.

If the heart rate was increased by less than 20% after the initial intravenous dose and the maximum serum concentration was less than 50 µg/l in the two first subjects a second intravenous dose (1/5 of the above defined threshold dose) should be given to totally eight subjects.

Subjects: 17 healthy male subjects 20-45 years of age, were enrolled in the study.

Blood and Urine Sampling: Blood samples were taken at 0, 0.33, 0.66, 1, 2, 3, 4, 6, 8, and 24 hours after administration except for the intravenous infusion when a 0.08 hour sample was added after 0.64 mg and a 0.17 hour sample after 1.28 mg. Urine were collected before the study during 24 hours and in portions at 0-24 and 24-48 hours after administration.

Analytical methodology:

RESULTS

Pharmacokinetics

A dose increase in the dose interval 3.2 mg to 12.8 mg (corresponding to 2.2 and 8.7 mg free base) resulted in an increase in the average maximum serum concentration from µg/l, i.e. a increase. For the same dose interval mean AUC increases from µg*h/l, i.e. a increase.

Seven serum samples showed levels over the limit of quantification after 24 hours; these samples have been excluded in the calculations in order to make half-life determination over comparable time frames for all subjects. The areas under the serum concentration time curve (AUC) up to the last time point of measurement has been added to the extrapolated area from the last time point of measurement to infinity. The following single dose pharmacokinetic parameters are also given: maximum serum concentration (C_{max}), time to peak (T_{max}), the elimination rate constant (k) and half-life ($t_{1/2}$). In the dose interval 3.2, 6.4 and 12.8 mg the mean value of C_{max} are 6.2, 9.6 and 25 µg/l occurring 0.7-1.1 hour after administration. The half-life is between 2.3 and 2.7 hours. AUC at corresponding doses are 27.6, 36.6 and 97.0 µg*h/l. After i.v. administration (1.28 mg) $t_{1/2}$ is 2.7 hours and V_d 113 l.

The estimations of mean bioavailability (F) are 39, 29 and 37 % at 3.2, 6.4 and 12.8 mg and the amount unchanged drug excreted in urine (A_e) for all subjects are 0.2-0.3% after oral administration and 0.8% after 1.28 mg intravenous administration.

Table 34. Mean (± SD) Pharmacokinetic Parameters

Parameter/ Dose	3.2 mg Oral Dose (n = 7)	6.4 mg Oral Dose (n = 8)	12.8 mg Oral Dose (n = 8)	0.64 mg IV Dose (n=2)	1.28 mg IV Dose (n=8)
C_{max} (µg/l)	6.2 ± 4.6	9.6 ± 6.0	25 ± 14	26	28 ± 12
T_{max} (h)	0.8 ± 0.2	0.9 ± 0.3	1.1 ± 0.59	0.1	----
k (1 /k)	0.26 ± 0.05	0.310 ± 0.074	0.312 ± 0.065	0.235	0.281 ± 0.072
$T_{½}$ (h)	2.7 ± 0.6	2.4 ± 0.69	2.3 ± 0.54	3.3	2.7 ± 1.3
AUC (µg * h/l)	27.6 ± 22.5	36.6 ± 26.7	97.0 ± 50.6	21.2	30.0 ± 7.95
CL_o (l/h)	120 ± 70.0	201 ± 143	124 ± 87.4	20.7	30.5 ± 6.57
Vd (L)	----	----	----	131	113 ± 22.9
F (%)	39	29	37	----	----

Pharmacodynamics

Heart rate

After the 3.2 mg dose an increase >20% was observed in three subjects); after the 6.4 mg dose in six subjects , and after the 12.8 mg dose in seven subjects . The maximum of the heart rate-time profiles (maximum of mean value profiles for subjects given 3.2, 6.4 and 12.8 mg, respectively) were +10%, +25% and +35% increase relative to the basal values. As described above ("Determination of intravenous dose") the threshold dose for effect on heart rate was found to be 6.4 mg.

After oral administration of 3.2 mg an increase in ≥20 beats/min was observed in one subjects at 6.4 mg in three subjects and after 12.8 mg in four subjects

Salivation

The mean effect on stimulated salivation was -9%, -42%, -28%, -64% and -92% after 0.8, 1.6, 3.2, 6.4 and 12.8 mg, respectively. These figures indicate that the pharmacological threshold dose for effect on salivation (<-20%) is 1.6 mg.

Near point of vision

The mean effect on near point of vision was +1%, +1% and +19% after 3.2, 6.4 and 12.8 mg, respectively. The pharmacological threshold dose for effect on near point of vision (>20%) is judged to be close to 12.8 mg.

Blood pressure

No significant change (i.e. >±20%) in either systolic or diastolic blood pressure was observed in any subject.

Clinical chemistry

The pre-study and post-study clinical chemistry variables were within the normal range throughout the study for all subjects except for No 6 whose ASAT values were slightly higher than average both pre-study and post-study.

Adverse reactions

Oral administration

At 0.2-1.6 mg no adverse effects were experienced and no signs were noticed.

At 3.2 mg 6 out of 8 subjects) reported dry mouth with an estimated duration of 1-4.5 hours, the symptom were occurring 20 minutes to 2 hours after administration. No subject showed any symptoms or signs of effect on the central nervous system.

At 6.4 mg 7 out of the 8 subjects clearly experienced dry mouth and/or dry throat (duration 2-5 hours), the symptomatology commencing 40 minutes to 2 hours after administration. Half of the subjects reported dry hands, starting at about the same time and of approximately the same duration as dry mouth. One subject experienced dry eyes lasting for about 1 hour and 45 minutes, appearing 2 hours after the intake of tolterodine. One subject reported a sensation of warmth straight across the central part of the face, appearing 24 minutes after dose and lasting for around 1.8 hours. One subject reported micturation difficulties, still present 4.75 hours after administration. No subject showed any symptoms or signs of effect on the central nervous system.

At 12.8 mg all subjects (8 out of 8) experienced dry mouth with or without dry throat (duration between about 4 to 9.5 hours), 40-60 minutes after administration. A few subjects reported dry hands, 4.5 to 8.5 hours of duration, starting 40 minutes to 1.5 hour after intake. Eye dryness were experienced by 2 subjects and three subjects reported accommodation problems with onset approximately 1 to 3 hours following administration. Two subjects showed gastrointestinal side effects One subject reported a sensation of warmth straight across the central part of the face, appearing 38 minutes after dose and lasting for around 4.7 hours. Six subjects showed prolonged micturation difficulties with an approximate duration of 4 to 16 hours after administration. No subject showed any symptoms or signs of effect on the central nervous system.

Intravenous infusion

At 0.64 mg 1 out of 2 subjects reported dry lips and a sensation of warmth in the face just like after previous oral administrations. The other subject reported micturation difficulties.

At 1.28 mg 3 out of 8 subjects experienced dry mouth (duration 45 min-3 hours) starting 30 minutes - 3 hours after infusion and 2 subjects reported micturation difficulties about 4.5 hours following infusion start. Subject exhibited the same reaction of warmth in the central region of the face as on previous occasions.

Sponsor's Conclusions

After single-dose administration the threshold dose for effect on heart rate is 6.4 mg, for effect on salivation 1.6 mg and for effect on near point of vision 12.8 mg.

After a dose increase approximate linear kinetics were obtained with respect to C_{max} and AUC.

APPEARS THIS WAY
ON ORIGINAL

Study Number: TRN 90-126-00

Title of the study: Disposition of [^{14}C]-labeled tolterodine after oral single-dose administration to healthy volunteers.

Objectives: To quantify the total recovery and routes of excretion of radioactivity after an oral dose of [^{14}C]-labeled tolterodine. To determine a urine metabolite profile in terms of chromatographic peaks from a HPLC-system in combination with a radiochemical detector.

Study Design: Single-dose, Open, non-comparative.

Subjects : 6 healthy male volunteers.

Product: [^{14}C]-labeled tolterodine (tolterodine L-tartrate) batch no. CA 006012 tolterodine batch no CA 005011. 5 mg oral solution (0.91 MBq).

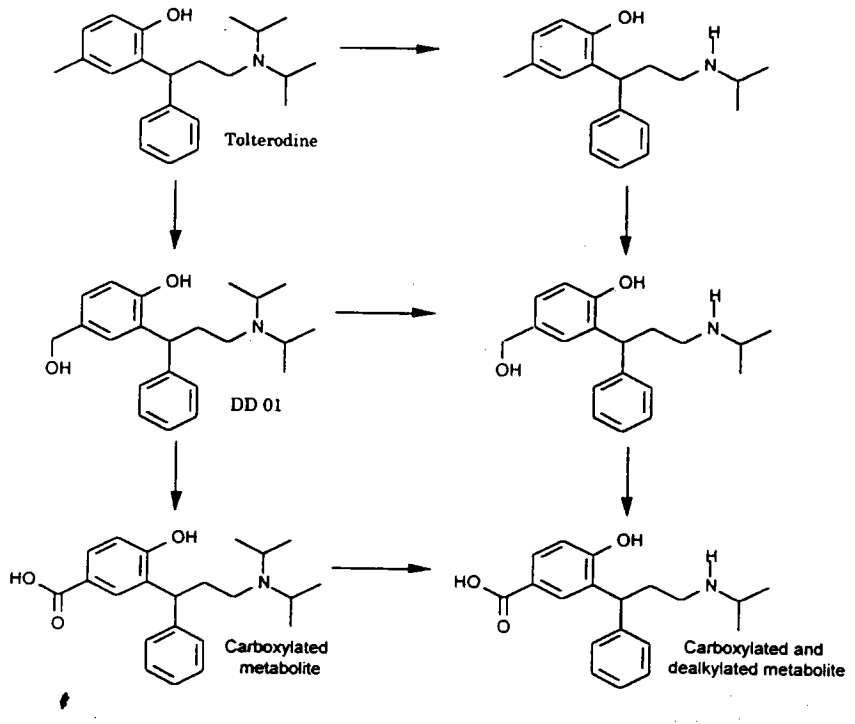


Figure 5. Identified urinary metabolites in man. All metabolites (and tolterodine)

The total recovery of radioactivity is given in Table 35. Within 7 days 94±2.5 % of the total amount of radioactivity was recovered. Of the [^{14}C]-tolterodine derived radioactivity 77±4.0% was recovered in urine and 17±3.5% in feces.

Table 35. Total excretion of radioactivity (7 days) after 5 mg oral administration of [^{14}C]-labeled tolterodine L-tartrate.

	Subject Number						Mean	S.D.
Urine (%)	79	71	74	79	81	80	77	4.0
Feces (%)	15	24	15	15	16	17	17	3.5
Total (%)	94	95	90	95	97	96	94	2.5

Table 36. Pharmacokinetic parameters of tolterodine and DD 01

	tolterodine								DD 01						
Subject No	C_{max} (µg/l)	t_{max} (h)	$t_{1/2z}$ (h)	AUC_0^- (µgh/l)	C_{av} (µg/l)	C_b/C_s	CL_o (l/h)	f_e (% of dose)	C_{max} (µg/l)	tmax (h)	$t_{1/2z}$ (h)	AUC_0^- (µgh/l)	C_{av} (µg/l)	C_b/C_s	f_e (% of dose)
	1.2	0.67	2.2	2.2	0.18	0.65	1582	<1.0	4.5	0.67	2.8	19	1.5	0.85	0.54
	8.4	1.0	3.7	50	4.1	0.67	69	<1.0	2.5	1.0	7.0	26	2.1	0.95	5.7
	12	1.0	4.0	66	5.5	0.57	52	<1.0	3.3	1.0	6.5	30	2.5	0.86	16
	15	0.67	1.7	32	2.6	0.53	108	<1.0	14	0.67	2.8	46	3.8	0.74	13
	1.2	0.67	2.0	2.6	0.21	0.56	1336	<1.0	4.6	0.67	2.6	18	1.5	0.79	3.8
	15	1.0	2.2	38	3.1	0.53	91	<1.0	9.0	1.0	3.7	43	3.5	0.70	4.3
Mean	8.7	0.84	2.6	32	2.6	0.59	540	n.a.	6.3	0.8	4.2	30	2.5	0.81	7.2
S.D.	6.3	0.18	0.96	25	2.1	0.09	717	n.a.	4.3	0.2	2.0	12	1.0	0.12	6.0

Sponsor's Conclusions:

- Within 7 days 94±2.5% of the [^{14}C]-tolterodine derived radioactivity was excreted in urine and feces in the six subjects.

- Of the total radioactive dose 77±4.0% was recovered in urine and 17±3.0% in feces.

- Less than 1% and 4.4±2.9% of the given dose was excreted as tolterodine and DD 01 in urine, respectively.

- The metabolite profiles in urine showed that more than 50% of the dose is excreted as "carboxylated metabolite" and "carboxylated and dealkylated metabolite".

Study Number: TRN 91-007-00

Study Title: Tolerability and Multiple-Dose Pharmacokinetics at Three Dose Levels of tolterodine Given Orally to Healthy Volunteers.

Study Objectives: The objectives of the present study were to:

- investigate the tolerability at multiple-dose administration.
- give an estimate of the degree of linearity within the dose interval 2.0 mg b.i.d., 4.0 mg b.i.d. and 6.0 mg b.i.d. using 2.0 mg tablets of tolterodine.
- measure heart rate, blood pressure, salivation and accommodation after multiple-dose administration.

Dosage and Administration: 2.0 mg tablets of tolterodine, Batch No 3010-0-A-1 manufactured by Pharmacia were used

In the first dose period one tablet was taken at 8 a.m. and one tablet at 8 p.m. On day 5 the last 2.0 mg dose was taken at 8 a.m. In the second dose period (start on day 22) 2 tablets were taken with the same interval as in the first period. In the third dose period (start on day 43) 3 tablets were taken with the same interval as in the first period.

Subjects: 4 healthy male subjects 20-50 years of age, were enrolled in the study.

Blood and Urine Sampling: Venous blood samples were collected before administration on day 1 and at 24, 48, 72 and 96 hours after the first 2.0 mg dose of tolterodine. Likewise blood samples were drawn at 24, 48, 72 and 96 hours after the first 4.0 mg dose (day 22) and 6.0 mg dose (day 43). After the last dose on each dosage regimen, i.e. in the morning on day 5, 26 and 47 a series of blood samples were taken at 0.5, 1, 2, 4, 8, 12, 16 and 24 hours, to establish the peak values at each dose level. Urine was collected quantitatively in portions at 0-12, 12-24 and 24-48 hours after the last administration at each dose level (day 5, 26 and 47).

Analytical Methodology:

RESULTS

Safety measurements: None of the safety registrations on heart rate and blood pressure, during the multiple-dose regimens, showed abnormal values in the four subjects.

Drop-outs: Subject No. 2 did not participate in the third multiple-dose regimen (6 mg b.i.d.) due to a non drug-related illness during the second wash-out period.

Pharmacokinetics

Linear kinetics at all three dose levels was evident in one of the four subjects while linearity up to 4 mg b.i.d. was apparent in subject The other two subjects showed almost unchanged C_{max} and AUC_{0-12} although the dose was increased.

One serum sample showed a level slightly over the limit of quantification after 16 hours; this sample has been excluded in the calculations in order to make half-life determinations over comparable time frames for all subjects. The following multiple-dose pharmacokinetic parameters are also given: maximum serum concentration (C_{max}), time to peak (T_{max})l elimination rate constant (k) and half-life ($t_{1/2}$) at the three dose levels 2 mg, 4 mg and 6 mg b.i.d.

Due to the extensive metabolism of the drug the low amount unchanged drug in urine neither confirm nor contradict the serum data concerning the degree of linearity.

Table 37. Mean Pharmacokinetic Parameters of Tolterodine after Oral Administration (DAY 5)

DOSE	2 mg b.i.d.	4 mg b.i.d.	6 mg b.i.d.
N	4	4	3
Cmax (µg/l)	2.8	4.2	6.6
Tmax (h)	0.9	1.1	0.7
k (1/h)	0.222	0.238	0.239
T½ (h)	3.2	3.0	2.9
AUC 0-12 h (µg h/l)	13.1	19.4	25.5

Pharmacodynamics

After 2 mg b.i.d. the average decrease in stimulated salivation was about 50%. Subject seemed to have a decrease in systolic blood pressure. No other significant disturbances on the effect parameters were noticed.

After 4 mg b.i.d. the average decrease in salivation was slightly more pronounced. Subject showed a transient decrease in systolic and diastolic blood pressure, -32%/-43%. No other significant disturbances on the effect parameters were noticed.

After 6 mg b.i.d. the average decrease in stimulated salivation was about -80%. Subject showed a general increased in heart rate. Some disparate results in diastolic blood pressure were measured. In subject an increase with 16% followed by a decrease with 25%, while in the other two subjects a slight increase was noticed.

Adverse reactions

At 2 mg b.i.d. two subjects out of four experienced micturation difficulties starting on day 3 and in the afternoon of day 2, respectively. In addition subject reported more frequent micturitions on days 2, 3 and 4 and on days 2 and 3, respectively. No other reactions were reported.

At 4 mg b.i.d. three of the four subjects reported problems discharging urine. In subject this was more or less pronounced at all micturitions from the first day, while subject only experienced voiding problems twice, and less frequent micturitions during all the 5 days. The duration of inhibited bladder function in subject was roughly estimated to 4-8 hours after drug administration. Dry mouth was experienced by all the four subjects; by in most instances together with dry eyes.

At 6 mg b.i.d. all subjects (3 out of 3) reported dry mouth and disturbed micturation. Two subjects experienced micturation difficulties during all the 5 days while subject reported more frequent micturation and difficulties holding the urine but difficulties voiding on only one occasion. Dry mouth generally commenced 1 hour after drug administration with an approximate duration of 1-6 hours. Subject also exhibited gastrointestinal disturbances (abdominal cramps and constipation, respectively).

Sponsor's Conclusions:

1. The three multiple-dose regimens (2, 4 and 6 mg b.i.d. for 5 days) were well tolerated. The clinical chemistry variables were within the normal range as well as the tests on liver enzymes.
2. The safety measurements on heart rate and blood pressure during the regimens did not reveal anything abnormal.
3. Linear kinetics within the whole dose range was evident in one subject while proportionality up to 4 mg b.i.d. was apparent in one additional subject. The remaining two subjects showed almost unchanged AUC and C_{max} with increasing dose.
4. The stimulated secretion of saliva was significantly inhibited with increasing dose. One subject showed an increase in heart rate at the highest dose.

After 6 mg b.i.d. all subjects reported micturation disturbances and two subjects had effects on the gastrointestinal-tract.

Reviewer's Comments:

1. The amount of unchanged drug eliminated in the urine was 0.1 - 0.2% of the administered dose.