

**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**Application Number 21-228**

**CLINICAL PHARMACOLOGY and**  
**BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology & Biopharmaceutics Review

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NDA:	21-228
Product Trade Name:	Detrol™ LA (Tolterodine Extended Release Capsules)
Active Ingredient/s:	Tolterodine tartarate
Indication:	
Submission Dates:	2/25/00 (original NDA), 10/20/00
Sponsor:	Pharmacia, Inc.
Type of Submission/Priority:	Original/3S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

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### Synopsis

In 1998, Detrol™ (tolterodine tartarate tablets) at doses of 1 and 2 mg BID was approved in the US for the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. In this current application, the sponsor seeks approval for 2 and 4 mg prolonged release capsules of tolterodine tartarate (tolterodine  $\cdot$ ) to be administered once daily. Data from clinical trials assessing safety and efficacy of tolterodine  $\cdot$  along with separate studies focussed on the clinical pharmacology and biopharmaceutics aspects have been provided.

### Recommendation

Based on the review, NDA 21-228 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. The suggested labeling changes are included in the section "Labeling Comments" and have been finalized, some of which are the same changes made while reviewing NDA 20-771 S002, S004, and S 007. There are no OCPB issues that remain unresolved currently with NDA 21-228.

*Comment to the sponsor:* The proposed ~~\_\_\_\_\_~~  
this will be taken at a future time.

*ISI*  
\_\_\_\_\_  
Dhruba J. Chatterjee, Ph.D.,  
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)  
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D.

*ISI*  
Dated- 11/16/00

CC: NDA 21-228, HFD 870 (H. Malinowski, A. Parekh, DJ. Chatterjee), HFD-580 (B. Gierhart, E. Farinas), CDR (B. Murphy). [A Briefing for NDA 21-228, held on 11/14 /2000, was attended by H. Malinowski, J. Hunt , A. Parekh and DJ. Chatterjee]

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## BACKGROUND

*Questions addressed in this section:*

- What is urinary incontinence?
- What is the pharmacologic rationale for use of this drug?
- What is the regulatory history of this product?
- What are other available alternatives?
- What CPB studies have been submitted in support of this NDA?

Urinary incontinence, the involuntary loss of urine, is a clinical problem. Urinary incontinence affects all age groups and is particularly common in the elderly. Overactive bladder is one cause of urinary incontinence. Overactive bladder is a condition characterized by involuntary detrusor contractions during the bladder filling phase, which may be spontaneous or provoked, and which the patient cannot suppress. Overactive bladder causes troublesome symptoms, which result in a significant impairment of normal social functioning. These symptoms include frequency, nocturia, urgency, and urge incontinence. Uncontrolled bladder contractions give the feeling of urgency, and exaggerated sense of needing to urinate. In turn, urgency causes frequency and nocturia; voiding at abnormally reduced intervals. Urgency may lead to urge incontinence if the sphincter mechanism is unable to resist the uncontrolled bladder contraction. Patients may have any combination of these symptoms. Frequency may be a primary symptom of the underlying disease or may be secondarily self-induced to avoid incontinence. Frequency and urgency mean that patients must make frequent visits to the toilet, so that daily activities are conditioned by the need to be near a toilet. Sleeping patterns are disrupted when these symptoms occur at night.

Urinary incontinence is not solely due to overactive bladder. Stress urinary incontinence, particularly common in women, is a type of urinary incontinence in which the urethral closure mechanism is compromised and urine escapes when intra-abdominal pressure increases sufficiently. Leakage may also occur as a result of a combination of overactive bladder and the compromised urethral closure mechanism. Patients sometimes present with symptoms of both urge and stress incontinence, called mixed incontinence. Mixed incontinence is common in women, especially older women. Involuntary loss of urine associated with overdistension of the bladder is termed overflow incontinence. Overflow incontinence may be caused by an underactive or acontractile detrusor, or may be due to bladder outlet or urethral obstruction leading to overdistension and overflow. Urine loss may be caused by factors outside the lower urinary tract, such as, chronic impairment of physical or cognitive functioning, or both, a condition termed as functional incontinence. Urine loss may also occur without any warning or sensory awareness, such as, in paraplegics and in some patients without overt neurologic dysfunction.

Normal bladder contractions are mediated primarily through cholinergic muscarinic receptor stimulation. These receptors are believed to control normal bladder contractions, and possibly play a major role in overactive bladders. Hence, antimuscarinic drugs have almost become a standard of therapy for overactive bladder. However, a most common side effect of these class of drugs is dry mouth (due to its effect on the salivary glands).

Tolterodine is a potent competitive muscarinic antagonist exhibiting some selectivity towards antimuscarinic activity at the bladder (in animal models). The FDA approved Tolterodine tartarate immediate release (IR) formulation at 1 and 2 mg BID doses in March 1998 for the management of overactive bladder. The current application seeks approval for once a day dosing of a tolterodine tartarate — formulation with an aim to minimize side effects of the drug due to a reduced fluctuations in its serum levels (as compared to IR).

Several drug therapies including antimuscarinics, antispasmodics, tricyclic antidepressants and estrogen are available to treat the disease. Prior to the availability of tolterodine, another antimuscarinic, oxybutynin (Ditropan) has been approved for the same indication. More recently an extended release formulation for oxybutynin (Ditropan XL) once-daily dosing has been approved by the FDA in December, 1998.

A total of 6 studies relating to clinical pharmacology and biopharmaceutics have been submitted in support of this application. These studies describe the formulation selection rationale, pharmacokinetics of the PR formulation from single dose and multiple doses, food effects and *in vitro* dissolution.

This review follows a 'Question-Based' approach.

## PHARMACOKINETICS

### Q. What is the PK profile of tolterodine from the IR formulation?

The general pharmacokinetics of tolterodine is described in sufficient detail in the Detrol™ physician's package insert. Since tolterodine is extensively metabolized in the liver leading to the formation of an active metabolite (5-hydroxymethyl tolterodine, DD 01), the PK of tolterodine and the active metabolite was studied in extensive (EM) and poor (PM) metabolizers. The following table summarizes the PK parameters of the two species in 8 EMs and 8 PMs following administration of Detrol (single and multiple doses, 4 mg BID).

Phenotype (CYP2D6)	Tolterodine					5-Hydroxymethyl Metabolite			
	t <sub>max</sub> (h)	C <sub>max</sub> * (µg/L)	C <sub>avg</sub> * (µg/L)	t <sub>1/2</sub> (h)	CL/F (L/h)	t <sub>max</sub> (h)	C <sub>max</sub> * (µg/L)	C <sub>avg</sub> * (µg/L)	t <sub>1/2</sub> (h)
Single-dose									
EM	1.6±1.5	1.6±1.2	0.50±0.35	2.0±0.7	534±697	1.8±1.4	1.8±0.7	0.62±0.26	3.1±0.7
PM	1.4±0.5	10±4.9	8.3±4.3	6.5±1.6	17±7.3	†	-	-	-
Multiple-dose									
EM	1.2±0.5	2.6±2.8	0.58±0.54	2.2±0.4	415±377	1.2±0.5	2.4±1.3	0.92±0.46	2.9±0.4
PM	1.9±1.0	19±7.5	12±5.1	9.6±1.5	11±4.2	-	-	-	-

\* Parameter was dose-normalized from 4 mg to 2 mg.

C<sub>max</sub> = Maximum plasma concentration; t<sub>max</sub> = Time of occurrence of C<sub>max</sub>;

C<sub>avg</sub> = Average plasma concentration; t<sub>1/2</sub> = Terminal elimination half-life; CL/F = Apparent oral clearance.

† = not applicable.

Following a 5-mg oral IR dose, Tolterodine was rapidly and almost completely ( $\approx 80\%$ ) absorbed. Food increased the bioavailability of IR tolterodine. The drug is highly bound to plasma proteins (primarily  $\alpha_1$ -glycoprotein) but the active metabolite is not.

Tolterodine is extensively metabolized in the liver (cytochrome P450, CYP 2D6), to an equipotent antimuscarinic 5-hydroxymethyl metabolite. Due to differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite is similar in EMs and PMs at steady state. Hence, the net pharmacologic activity of tolterodine is expected to be similar in extensive and poor metabolizers, and a dose adjustment is not recommended in the Detrol™ label for PMs.

Following administration of a 5-mg IR oral dose of  $^{14}\text{C}$ -tolterodine to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as the active 5-hydroxymethyl metabolite.

For a more detailed review of the pharmacokinetics of tolterodine and its active metabolite, the reader may refer to the Dr. Gary Barnette's Clinical Pharmacology and Biopharmaceutics review of NDA 20-771 (dated March 12, 1998).

**Q. What are the PK characteristics of tolterodine from single and multiple doses of the PR formulation? How does this compare to the IR formulation?**

**(i) Single Dose**

The sponsor conducted clinical Study 98-TOCR-010 (details Attachment I), which provides the following information; a) comparison of PK profiles of tolterodine following single doses of the IR and PR formulations and b) effect of food (a standardized high-fat breakfast) on the PK of tolterodine from the PR doses.

**Results:**

**Table 1. Pharmacokinetic parameters (median with range in first row and mean with SD in second row) for the active moiety (n=17)**

Parameter	Treatment		
	PR capsule fed 8 mg	PR capsule fasted 8 mg	IR tablet fasted 4 mg
AUC <sub>0-∞</sub> (nM·h)	38 (14 - 76) 42.8 (17.6)	42 (16 - 72) 43.9 (15.1)	22 (14 - 45) 25.1 (8.8)
AUC <sub>0-t</sub> (nM·h)	38 (14 - 74) 41.7 (17.5)	41 (16 - 71) 42.8 (14.8)	22 (14 - 43) 24.5 (8.4)
C <sub>max</sub> (nM)	2.5 (0.66 - 4.8) 2.6 (1.0)	3.0 (0.58 - 4.7) 2.9 (1.1)	5.0 (1.9 - 8.1) 5.2 (1.6)
t <sub>lag</sub> (h)	1 (0.5 - 2)	0 (0 - 0.5)	0 (0 - 0)
t <sub>max</sub> (h)	6 (4 - 12)	4 (3 - 6)	0.75 (0.5 - 1)
t <sub>1/2</sub> (h)	8.6 (4.2 - 26) 8.9 (4.7)	6.7 (3.6 - 29) 8.0 (5.8)	3.7 (2.4 - 9.9) 4.1 (1.8)

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**Table 2. Pharmacokinetic parameters (median with range in first row and mean with SD in second row) for tolterodine in the extensive metabolizers (n=16).**

Parameter	Treatment		
	PR capsule fed 8 mg	PR capsule fasted 8 mg	IR tablet fasted 4 mg
AUC <sub>∞</sub> (µg/h)	23 (13 - 107)	27 (10 - 111)	12 (3.4 - 68)
	37.3 (29.0)	37.0 (27.6)	19.6 (17.2)
AUC <sub>0-∞</sub> (µg/h)	23 (12 - 106)	26 (9.5 - 110)	11 (2.9 - 67)
	35.4 (28.9)	35.3 (27.6)	19.2 (17.2)
C <sub>max</sub> (µg/l)	1.8 (0.91 - 5.9)	2.3 (0.82 - 6.2)	4.3 (1.2 - 15.1)
	2.5 (1.5)	2.7 (1.6)	5.4 (3.8)
t <sub>lag</sub> (h)	1 (0.5 - 2)	0 (0 - 0.5)	0 (0 - 0)
t <sub>max</sub> (h)	4 (3 - 12)	4 (2 - 6)	0.75 (0.5 - 1.5)
t <sub>1/2</sub> (h)	8.1 (3.3 - 27)	7.9 (4.0 - 13)	2.4 (1.6 - 4.6)
	10.6 (6.7)	8.4 (3.2)	2.8 (1.1)

**Table 3. Pharmacokinetic parameters (median with range in first row and mean with SD in second row) for DD 01 in the extensive metabolizers (n=16).**

Parameter	Treatment		
	PR capsule fed 8 mg	PR capsule fasted 8 mg	IR tablet fasted 4 mg
AUC <sub>∞</sub> (µg/h)	42 (19 - 88)	50 (32 - 87)	27 (18 - 50)
	46.2 (17.0)	49.1 (15.2)	27.2 (8.7)
AUC <sub>0-∞</sub> (µg/h)	41 (18 - 87)	49 (31 - 86)	26 (17 - 48)
	45.1 (17.1)	47.6 (15.2)	26.3 (8.3)
C <sub>max</sub> (µg/l)	2.8 (1.5 - 4.4)	3.1 (1.7 - 5.2)	5.5 (3.4 - 7.6)
	2.8 (0.8)	3.2 (1.0)	5.5 (1.2)
t <sub>lag</sub> (h)	1 (0.5 - 2)	0 (0 - 0.5)	0 (0 - 0)
t <sub>max</sub> (h)	6 (4 - 12)	4 (3 - 6)	0.75 (0.5 - 1)
t <sub>1/2</sub> (h)	8.5 (4.3 - 11)	7.2 (4.2 - 29)	3.8 (2.5 - 6.0)
	8.1 (2.2)	8.8 (5.9)	3.7 (0.93)

**Table 4. Relative bioavailability (F<sub>rel</sub>), based on AUC<sub>∞</sub>, Geometric mean with 90% confidence intervals.**

		Capsule fed vs. Capsule fasted	Capsule fasted vs. IR tablet <sup>1</sup>
		Active moiety	Geom. mean 90% CI
DD 01	Geom. mean 90% CI	0.94 0.86 - 1.01	0.90 0.87 - 0.94
Tolterodine	Geom. mean 90% CI	1.00 0.89 - 1.11	0.98 0.87 - 1.10

<sup>1</sup>: Corrected for differences in dose

**Table 5. Relative bioavailability ( $F_{ra}$ ), based on  $AUC_{last}$ , Geometric mean with 90% confidence intervals.**

		Capsule fed vs. Capsule fasted	Capsule fasted vs. IR tablet <sup>1</sup>
Active moiety	Geom. mean	0.95	0.86
	90% CI	0.87 - 1.04	0.80 - 0.93
DD 01	Geom. mean	0.94	0.90
	90% CI	0.86 - 1.03	0.87 - 0.94
Tolterodine	Geom. mean	0.99	0.96
	90% CI	0.88 - 1.12	0.85 - 1.08

1: Corrected for differences in dose

**Table 6.  $C_{max}$  ratios - Geometric mean with 90% confidence intervals.**

		Capsule fed 8 mg vs. Capsule fasted 8 mg	Capsule fasted 8 mg vs. IR tablet 4 mg
Active moiety	Geom. mean	0.91	0.53
	90% CI	0.78 - 1.06	0.45 - 0.63
DD 01	Geom. mean	0.88	0.57
	90% CI	0.75 - 1.03	0.49 - 0.66
Tolterodine	Geom. mean	0.98	0.48
	90% CI	0.84 - 1.14	0.41 - 0.57

Figure 1. Median serum concentrations of DD 01 in extensive metabolizers (n=16).

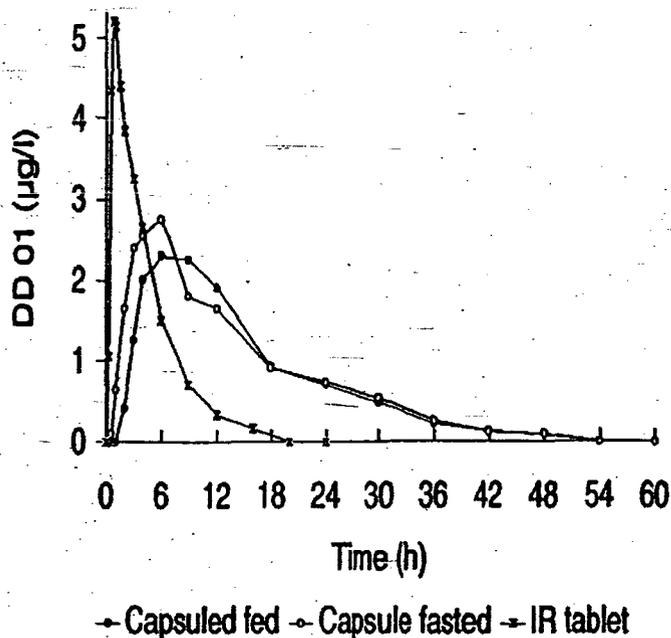
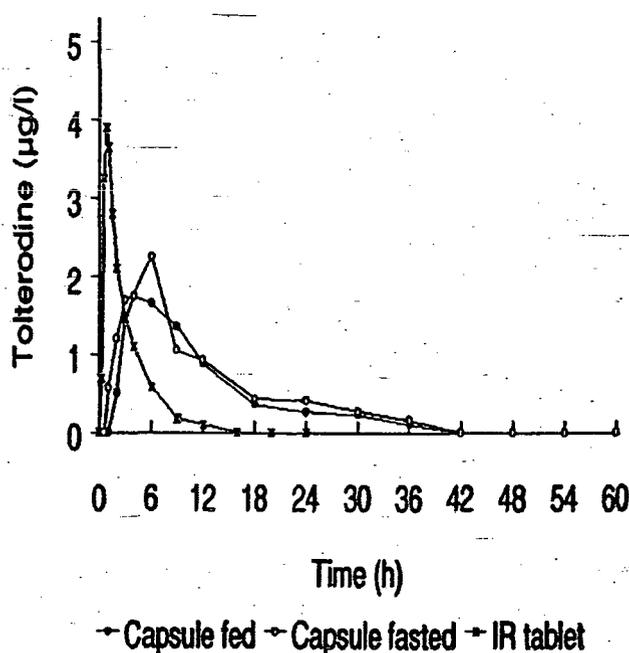


Figure 2. Median serum concentrations of tolterodine in extensive metabolizers (n=16).



**Reviewer's Comments**

- This study used twice the recommended dose for both PR and IR formulations for ease of drug assay and PK analysis. However, this may not affect the comparative nature of PK conclusions between the two formulations as well as fed and fasted states.
- From the data above, it appears that for the active moiety, DD 01, and tolterodine there was equivalence in AUC (both  $AUC_{\infty}$  and  $AUC_{last}$ ) when the two capsule administrations were compared to each. Hence, no food effect was seen.
- Based on  $C_{max}$ , the confidence intervals for the ratios for the fed vs. fasted capsule administration was within 0.75 – 1.14 (for all species analyses). This might indicate that the fed state may have a minor effect towards a reduction in rate of absorption, but this may not be clinically significant.
- No sign of 'dose dumping' was evident from the PK profiles of the PR formulation, or due to the effect of food.
- Equivalence was seen for AUC (both  $AUC_{\infty}$  and  $AUC_{last}$ ) for the active moiety, DD 01 and tolterodine, when comparing the PR capsule with the IR tablet.
- Sponsor reports that 'the bioavailability of the PR capsule, relative to the IR tablet, in the poor metabolizer was approximately 50%'. Since this was only from one subject, no conclusion can be drawn from this result about the clinical relevance of this finding.
- $C_{max}$  for the capsule, compared to the IR tablet, was significantly reduced even though twice as high a dose was used for the capsule. This was expected and, in fact one desired characteristics for the PR formulation. The other desired characteristic is being fulfilled by a significant increase in the apparent  $t_{1/2}$  of the active moiety from the PR formulation as compared to the IR.
- Examination of the mean serum drug concentration profile (and a majority of the 17 individual profiles) indicates that in comparison with the IR, the PR formulation is effective in increase of the  $T_{max}$ , decrease of the  $C_{max}$  while maintaining bioequivalence. Hence, it fulfills the main criteria for an extended release formulation.

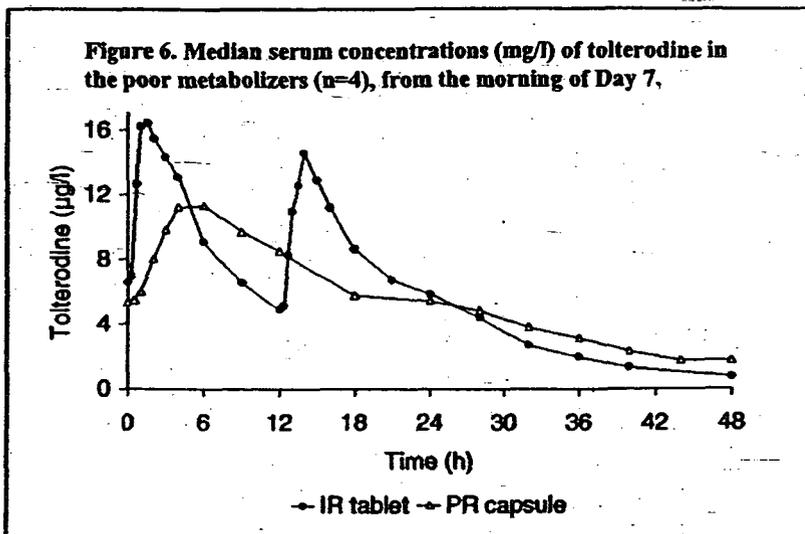
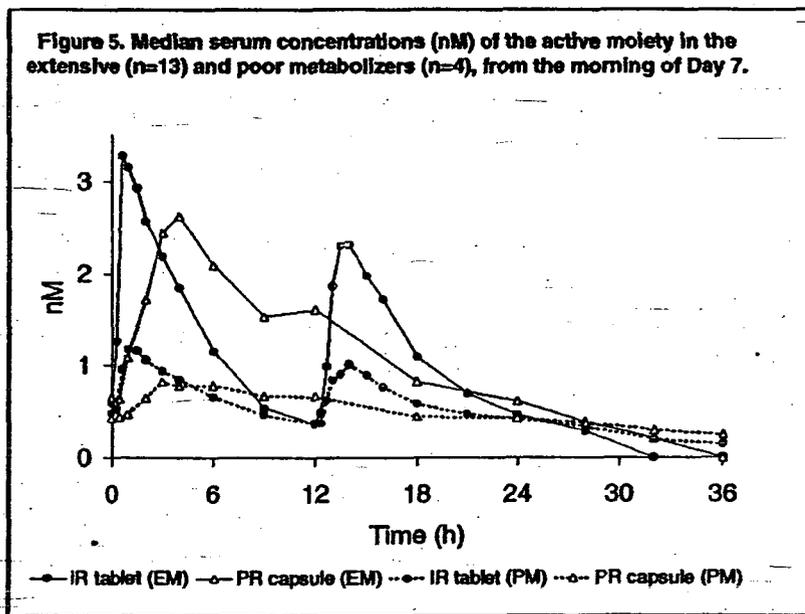
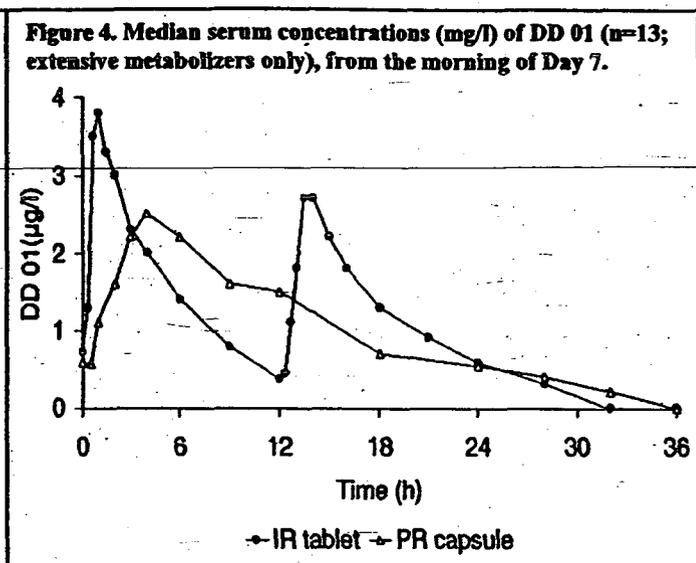
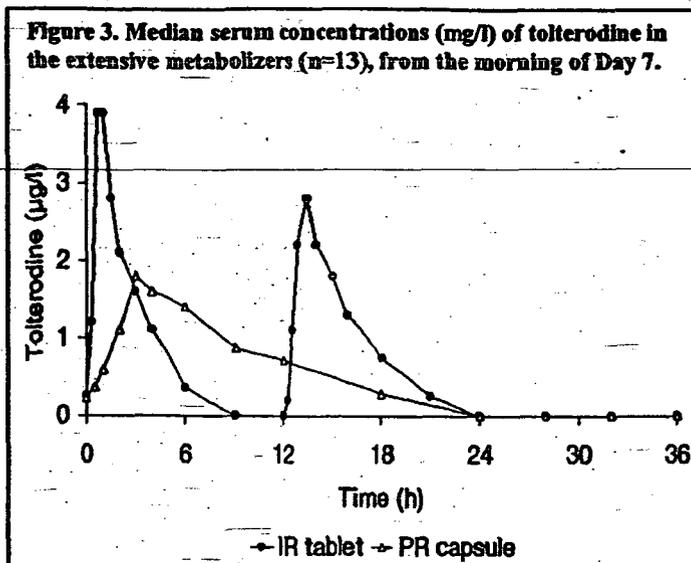
**(ii) Multiple Dose**

The sponsor conducted clinical Study 97-TOCR-006 (details Attachment II), which provides the following information:

- Comparison of PK profiles of tolterodine at steady state following multiple doses of the IR and PR formulations
- Comparison of the change of salivation (side effect) profile from baseline between IR and PR dosing

**Results:**

The following figures and tables illustrate the comparative PK of tolterodine, DD 01 and the active moiety following IR and PR dosing. Results following the salivation data analysis will be described in the next section (pharmacodynamics).



**Table 7. Pharmacokinetic parameters for (A) tolterodine and (B) DD 01 and (C) active moiety (medians with range in first row and means with SD in second row #).**

(A) Tolterodine					(B) DD 01				
Parameter	Treatment				Parameter	Treatment			
	PR capsule		IR tablet			PR capsule		IR tablet	
	EMs (n=13)	PMs (n=6)	EMs (n=13)	PMs (n=6)		EMs (n=13)	PMs (n=6)	EMs (n=13)	PMs (n=6)
AUC <sub>0-24</sub> (ng/h)	17.0 (5.5 - 256) 40.5 (67.5)	186 (156 - 717) 311 (271)	28.0 (3.8 - 233) 42.1 (61.3)	223 (175 - 691) 328 (243)	AUC <sub>0-24</sub> (ng/h)	32 (13 - 64) 33.4 (13.8)	n.d. n.d.	36 (14 - 68) 38.8 (17.1)	n.d. n.d.
C <sub>max</sub> (ng/ml)	2.0 (0.35 - 18.2) 3.4 (4.8)	11.5 (8.1 - 42.4) 18.8 (15.5)	4.8 (0.48 - 18.5) 5.3 (5.0)	18.5 (13.1 - 46.4) 23.1 (15.7)	C <sub>max</sub> (ng/ml)	2.5 (1.0 - 4.3) 2.7 (0.90)	n.d. n.d.	3.8 (1.8 - 6.6) 4.0 (1.5)	n.d. n.d.
C <sub>min</sub> (ng/ml)	0.11 (0.01 - 6.1) 0.70 (1.7)	5.0 (4.0 - 23) 9.3 (9.3)	0.07 (0.002 - 4.7) 0.50 (1.3)	4.9 (4.0 - 21) 8.7 (8.2)	C <sub>min</sub> (ng/ml)	0.54 (0.03 - 1.5) 0.60 (0.40)	n.d. n.d.	0.37 (0.06 - 1.4) 0.50 (0.40)	n.d. n.d.
FI	2.0 (0.91 - 4.1) 2.2 (0.90)	0.78 (0.62 - 0.96) 0.80 (0.20)	3.5 (1.4 - 5.9) 3.6 (1.2)	1.2 (0.88 - 1.5) 1.2 (0.20)	FI	1.5 (0.72 - 2.9) 1.8 (0.70)	n.d. n.d.	2.6 (0.74 - 4.0) 2.4 (0.90)	n.d. n.d.
t <sub>max</sub> (h) <sup>#</sup>	4 (2 - 6)	4 (3 - 6)	n.d.	n.d.	t <sub>max</sub> (h) <sup>#</sup>	4 (2 - 6)	n.d.	n.d.	n.d.
t <sub>1/2</sub> (h)	6.2 (3.2 - 14) 6.9 (3.5)	11 (8.9 - 41) 18.0 (15.5)	2.8 (1.8 - 8.1) 3.5 (2.1)	8.7 (7.6 - 17) 10.5 (4.5)	t <sub>1/2</sub> (h)	10 (3.1 - 18) 9.9 (4.0)	n.d. n.d.	5.0 (3.2 - 13) 5.3 (2.6)	n.d. n.d.

# Only medians with range are presented for t<sub>max</sub>.

\* The overall C<sub>max</sub>, i.e., the highest concentration found (morning or evening) is presented here for the IR tablet. Descriptive statistics for the overall t<sub>max</sub> have not been calculated for the tablets. Descriptive statistics for morning and evening C<sub>max</sub> and t<sub>max</sub> are found in Section 13.2.3.

# Only medians with range are presented for t<sub>max</sub>.

\* The overall C<sub>max</sub>, i.e., the highest concentration found (morning or evening) is presented here for the IR tablet. Descriptive statistics for the overall t<sub>max</sub> have not been calculated for the tablets. Descriptive statistics for morning and evening C<sub>max</sub> and t<sub>max</sub> are found in Section 13.2.3.

**(C) Active moiety**

Parameter	Treatment					
	PR capsule			IR tablet		
	EMs (n=13)	PMs (n=6)	All (n=17)	EMs (n=13)	PMs (n=6)	All (n=17)
AUC <sub>0-24</sub> (nM/h)	31 (13 - 52) 32.5 (11.7)	14 (13 - 52) 23.3 (19.2)	26 (13 - 52) 30.4 (13.7)	32 (14 - 60) 33.7 (13.1)	15.5 (14 - 45) 22.5 (15.0)	28 (14 - 60) 31.1 (13.9)
C <sub>max</sub> (nM)	2.7 (1.0 - 3.7) 2.6 (0.80)	0.85 (0.77 - 3.1) 1.4 (1.1)	2.7 (0.77 - 3.7) 2.3 (1.0)	3.8 (1.8 - 5.5) 3.6 (1.0)	1.2 (1.0 - 3.0) 1.8 (0.90)	3.2 (1.0 - 5.5) 3.1 (1.3)
C <sub>min</sub> (nM)	0.81 (0.03 - 1.2) 0.60 (0.40)	0.40 (0.30 - 1.7) 0.70 (0.70)	0.53 (0.03 - 1.7) 0.60 (0.40)	0.11 (0.01 - 6.1) 0.70 (1.7)	5.0 (4.0 - 23) 9.3 (9.3)	0.32 (0.01 - 23.2) 2.7 (5.7)
FI	1.8 (0.82 - 3.0) 1.7 (0.70)	0.76 (0.62 - 0.96) 0.80 (0.20)	1.4 (0.62 - 3.0) 1.5 (0.70)	2.7 (0.84 - 4.1) 2.5 (0.80)	1.2 (0.88 - 1.5) 1.2 (0.20)	2.2 (0.88 - 4.1) 2.2 (0.90)
t <sub>max</sub> (h)	4 (2 - 6)	4 (3 - 6)	4 (2 - 6)	n.d.	n.d.	n.d.
t <sub>1/2</sub> (h)	8.8 (3.0 - 18) 9.5 (4.0)	11 (8.9 - 66) 24.2 (27.9)	9.0 (3.0 - 66) 13.0 (14.1)	4.8 (3.2 - 12) 5.1 (2.3)	3.9 (7.8 - 17) 10.6 (4.3)	5.3 (3.2 - 17) 6.4 (3.7)

# Only medians with range are presented for t<sub>max</sub>.

\* The overall C<sub>max</sub>, i.e., the highest concentration found (morning or evening) is presented here for the IR tablet. Descriptive statistics for the overall t<sub>max</sub> have not been calculated for the tablets. Descriptive statistics for morning and evening C<sub>max</sub> and t<sub>max</sub> are found in Section 13.2.3.

**Table 8. AUC<sub>24</sub>, C<sub>max</sub> and C<sub>min</sub> ratios for the PR capsule relative to the IR tablet. Geometric mean with 90% confidence intervals.**

	AUC <sub>24</sub>	C <sub>max</sub>	C <sub>min</sub>
Tolterodine (n = 17)	0.91 (0.78 - 1.07)	0.61 (0.49 - 0.76)	1.83 (1.06 - 3.15)
DD 01 (n = 13)	0.88 (0.78 - 0.99)	0.67 (0.57 - 0.79)	1.32 (0.90 - 1.92)
Active moiety (n = 17)	0.97 (0.90 - 1.04)	0.74 (0.65 - 0.84)	1.43 (0.55 - 3.76)

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**Reviewer's comments:**

- The PR capsule showed acceptable release properties with  $C_{max}$  levels of approximately 50 - 75% (tolterodine, DD 01 and active moiety) for the PR capsule compared to the IR tablet.  $C_{min}$  levels were about 1.5 times higher for the PR capsule. The fluctuation index was consequently lower for the PR capsule than the IR tablet.
- $AUC_{24}$  for the active moiety was shown to be equivalent for the PR capsules and IR tablets. However, the  $AUC_{24}$  ratios for tolterodine and DD 01 did not quite meet the generally accepted equivalence criteria (missed narrowly - 90% CI between 0.78 - 1.07). There may be a variety of reasons for this, which may not necessarily be a major issue clinically.
- All other metabolites of tolterodine (other than DD 01) showed similar levels between the PR and the IR dosage forms.
- Comparing  $C_{max}$  across studies between the single dose data (and correcting for half the administered dose) with the multiple dose data, an approximate accumulation factor of 2 - 3 is obtained at steady state (for the active moiety).
- The data here (figure 5 above) *does not show* that 'the sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite ("active moiety") is similar in extensive and poor metabolizers' as claimed in the label. The label was modified accordingly.
- Medical officer notes that in the pivotal clinical trial, the extended release dosage form was administered in the morning. A mention of that is recommended in relevant sections of the label.

## PHARMACODYNAMICS

**Q. What is the general pharmacodynamic response profile for tolterodine?**

Tolterodine is a potent muscarinic antagonist used to treat urinary incontinence. Its use in patients lead to a reduction in number or incontinence episodes per week, a reduction in the number of micturations per day, an increase in the volume voided per micturation, and an increase in the residual urine volume. Dry mouth (most frequent), constipation, abnormal vision (accommodation abnormalities), urinary retention and dry eyes are expected side effects of tolterodine.

**Q. Was the correct dose selected for the tolterodine PR capsules?**

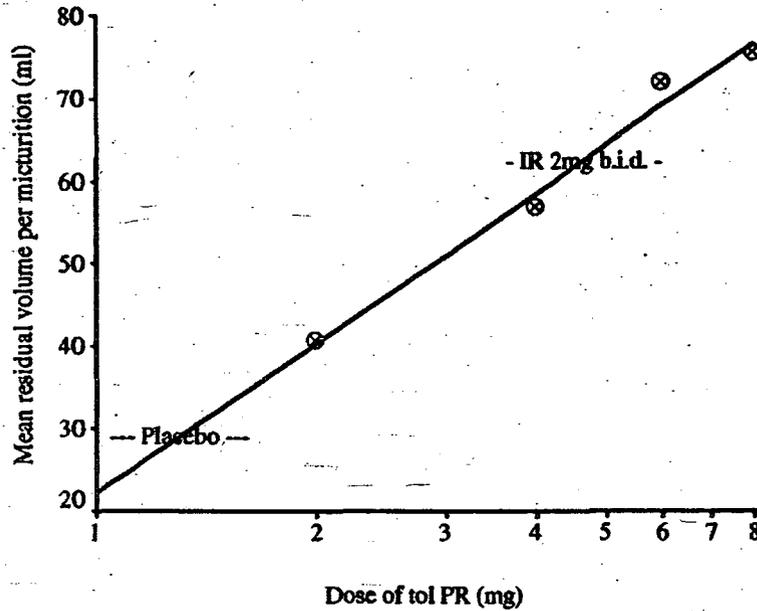
Sponsor conducted a dose-finding trial (Study # 97-TOCR-002) and a PK-PD analysis to decide which among the 2, 4, 6 or 8 mg PR capsule doses is equivalent to the 2 mg BID IR tablet in terms of efficacy and safety. Details of the study method etc. are provided in Attachment III. Note that the PR formulations used for this study were 'non-final' formulations, and were roughly 70% bioequivalent to the IR formulation. This was used to make dose corrections when comparing the IR and these 'non-final' formulations.

The sponsor used a model to establish the dose-effect relationship and the equivalent PR dose to match the efficacy/safety of the 2 mg BID IR (marketed) formulation.

**Results**

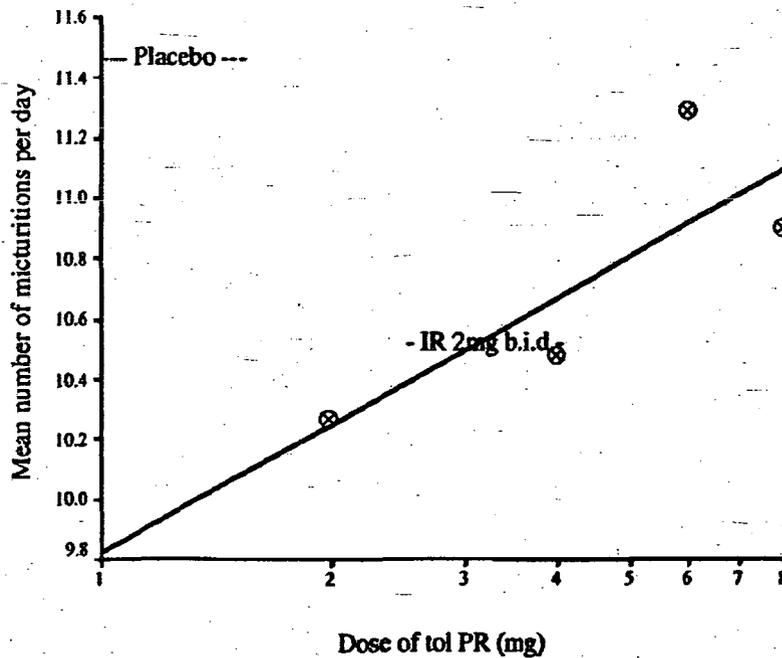
a) **Efficacy:** Figure 7 and 8 show the dose-effect relationship for the 5 treatments.

**Figure 7. The dose-effect relationship of tol PR (straight line) and least square means  $\alpha$  for tol IR tablet, placebo and tol PR 2, 4, 6 and 8 mg ( $\otimes$ ).**



$\alpha$  from model without restriction to a linear dose-effect relationship.

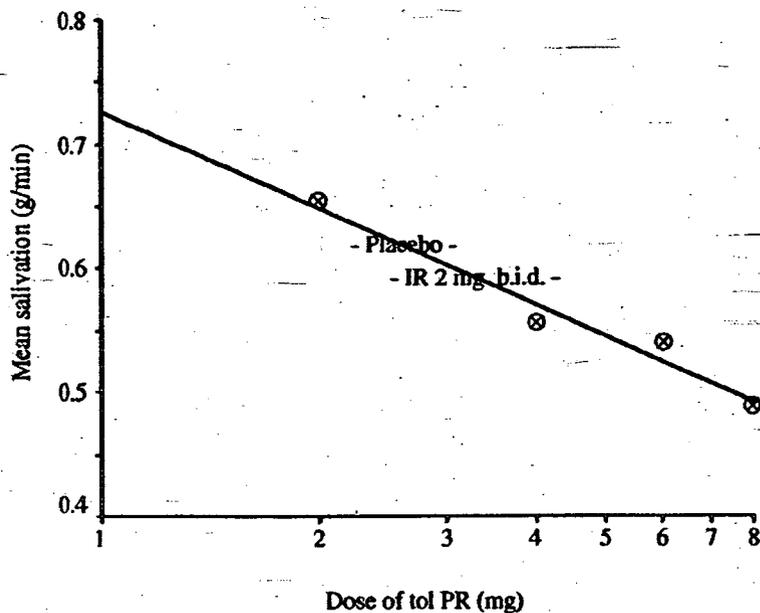
**Figure 8. The dose-effect relationship of tol PR (straight line) and least square means  $\alpha$  for tol IR tablet, placebo and tol PR 2, 4, 6 and 8 mg ( $\otimes$ ).**



$\alpha$  from model without restriction to a linear dose-effect relationship.

b) Safety

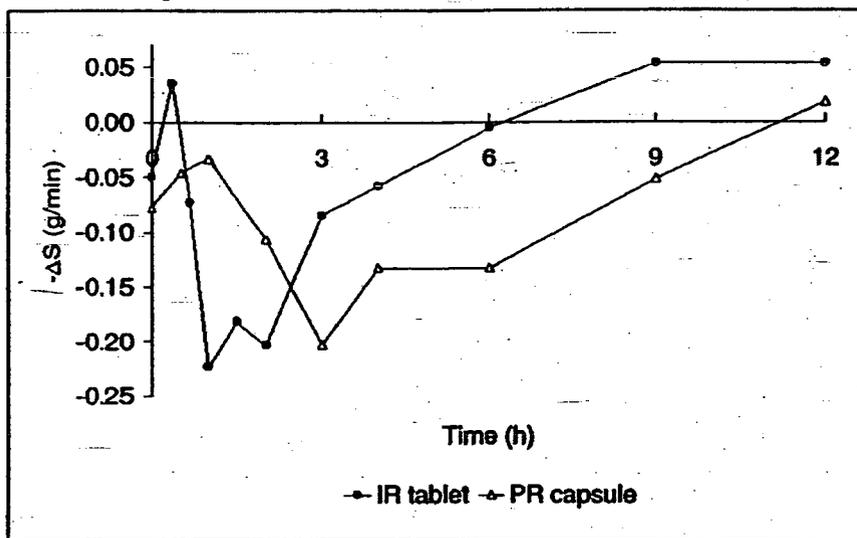
Figure 9. The dose-effect relationship of tol PR (straight line) and least square means <sup>a</sup> for tol IR tablet, placebo and tol PR 2, 4, 6 and 8 mg (⊗).



<sup>a</sup> from model without restriction to a linear dose-effect relationship.

With the final formulations, the sponsor conducted a comparison of salivation between the PR and IR formulations (Study 97-TOCR-006, Attachment II), and presents the following Figure 10.

Figure 10. The median change in salivation from baseline (-DS) during treatment with tolterodine tartrate PR capsules 4 mg once daily and IR tablets 2 mg twice daily (n=17).



### Reviewer's Comments

- Based on residual volume, the sponsor calculated that 3.7 mg was the effective dose of the PR formulation equivalent to the 2 mg BID IR dose (also considering the lowered bioequivalence of the 'non-final' formulation used).
- Mean number of micturation from 4 mg PR dose was comparable to that from that from the 2 mg BID IR dose. Other secondary efficacy parameters (for which data was not modeled) such as number of incontinence episodes per 24 hours was comparable between the 4 mg PR and the 2 mg BID IR doses, while mean voided volume/micturation is higher at the higher (6 and 8 mg) PR doses.
- Reviewing the reported data on adverse events, it appeared that both the 2 and 4 mg PR doses reduced both general side effects as well as dry mouth. Adverse events from the 6 and 8 mg PR doses were appreciably higher, and there is a chance of higher incidences of urinary retention. Hence, the choice of 4 mg as the highest PR dose is deemed appropriate.
- Figure 10 above shows that with the final PR formulation, there is (to say the least) no obvious advantage from the perspective of salivation as compared to the IR dosage. What may be concluded is that, dry mouth may persist till approximately half the dosing interval (6 hours for BID IR and 12 hours for QD PR).

## BIOPHARMACEUTICS

**Q. Is the to-be-marketed formulation same as the one used for the Phase III clinical trials?**

Yes. Please see attachment IV (Amendment 9 to this NDA sent at OCPB's request on 10/30/00) which also contains the final formulation (4 mg extended release).

**Q. Is the dissolution profile for the final formulation acceptable in terms of *in vitro* dissolution rate specification and IVIVC?**

Although currently the sponsor does not require showing evidence that IVIVC exists for the PR formulation, development of such a model may be advantageous in the future (for formulation changes etc.). The sponsor has conducted two studies to develop a Level A IVIVC and get an idea about setting dissolution specifications.

- One study (# 97-TOCR-003) determines the *in vitro* dissolution profiles and relative bioavailabilities of 4 different PR capsules as compared to a solution formulation (results not reported in this review). They concluded that with decreasing *in vitro* (and *in vivo*) dissolution rate there was a decrease in relative bioavailability compared to the solution. This indicates that the absorption from the slowest releasing capsules is incomplete. The two faster releasing capsules showed acceptable bioavailability in this single dose trial. Based on DD 01 there was a good rank order correlation between *in vitro* dissolution rate and PK parameters.

- In another study (Study # 97-TOCR-005) using 14 subjects, the sponsor developed an IVIVC model with 4 different PR capsule prototypes (at different *in vitro* dissolution rates). The prototypes were  $\alpha$  (fast rate),  $\beta$  (intermediate rate),  $\gamma$  (slow rate) and  $\delta$  (portion of  $\beta$  stored at 40 degrees C and 75% R.H. for a month showing differential dissolution rates in 2 different media). The following are the results in graphical plots:

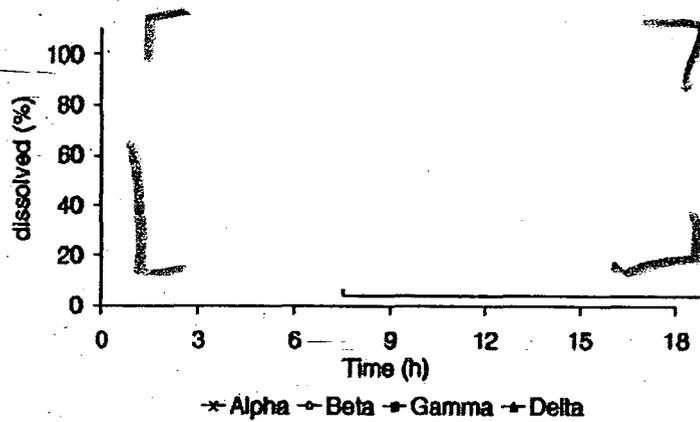
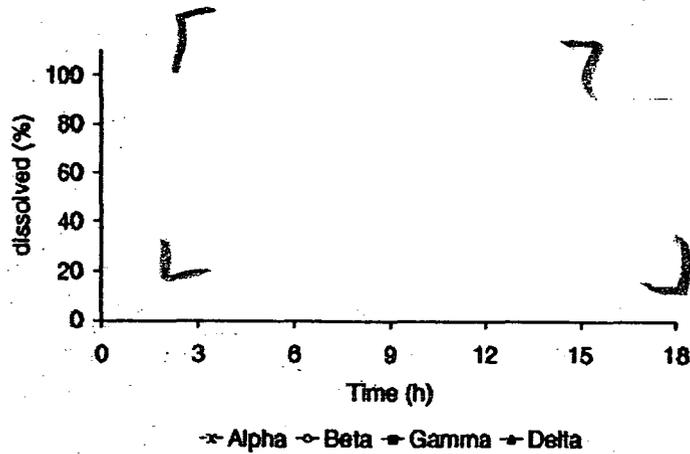
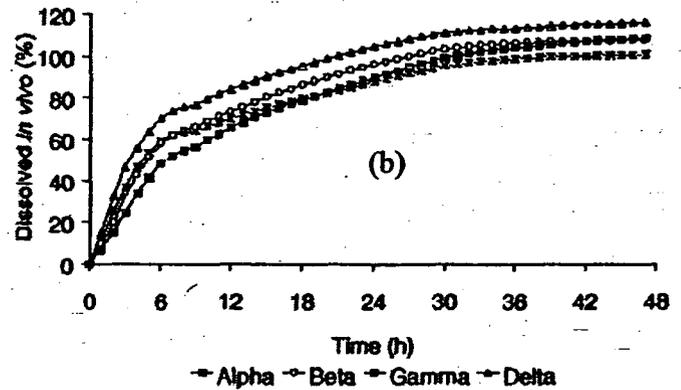
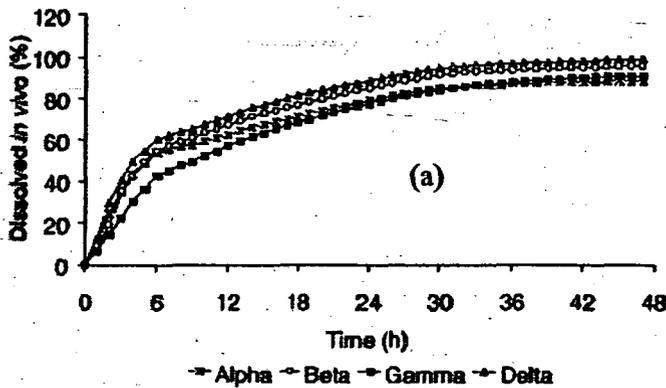
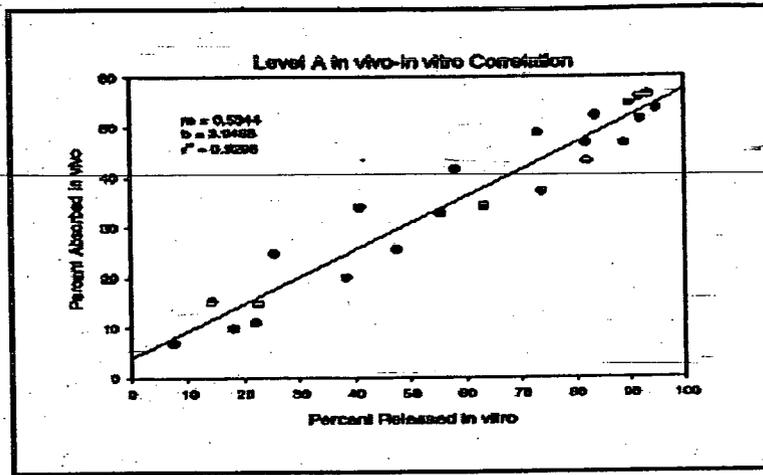


Figure 13. Mean in vivo dissolution rates (n=14) for the 4 capsules based on (a) DD 01 data and (b) tolterodine data.



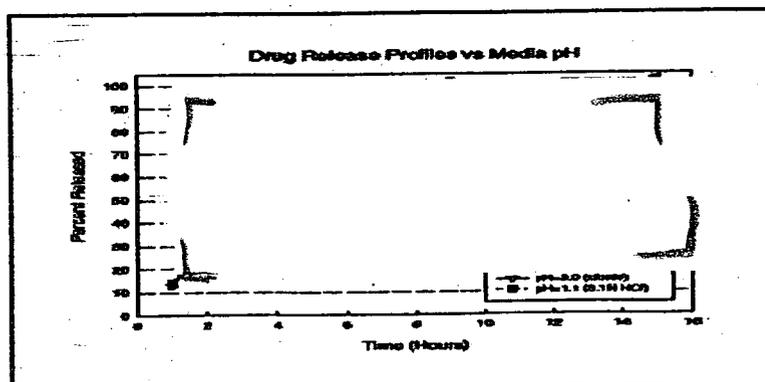


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**Reviewer's Comments**

- Using a convolution technique the sponsor shows an IVIVC correlation. They conclude that (a) *in vitro* dissolution rates at least as gamma PR capsule should be bioequivalent to the IR tablet (since all these PR capsules were bioequivalent to the IR tablet) and (b) the *in vivo* dissolution rate best correlates to the *in vitro* dissolution in the regular USP buffer, without addition of KCl.
- However, it is to be noted that the 4 capsule formulations were bioequivalent (compared to IR for AUC) only for DD 01, and generally exceeded the accepted BE range (0.8 – 1.25) with respect to tolterodine. The sponsor found that tolterodine levels are generally very variable and the effect of food on tolterodine absorption becomes a difficult and confounding factor, so they arrived to their conclusions based on DD 01 data. The appropriateness of developing an IVIVC based on just the metabolite data may be questionable. Also, only EMs were been used in these studies (for simplicity).
- The sponsor does present in detail a Level C and Level A IVIVC model (with internal and external prediction errors). A detailed review of the IVIVC analysis currently ongoing and a decision of acceptability of the analysis will be made at a later time. IVIVC analysis is not critical for decisions related to this NDA since the formulation in the pivotal clinical trial will be same as the marketed formulation.
- The relationship of dissolution to the pH of dissolution medium is shown in the figure below:

Figure 11.3. Drug-release Profiles vs. Medium pH.



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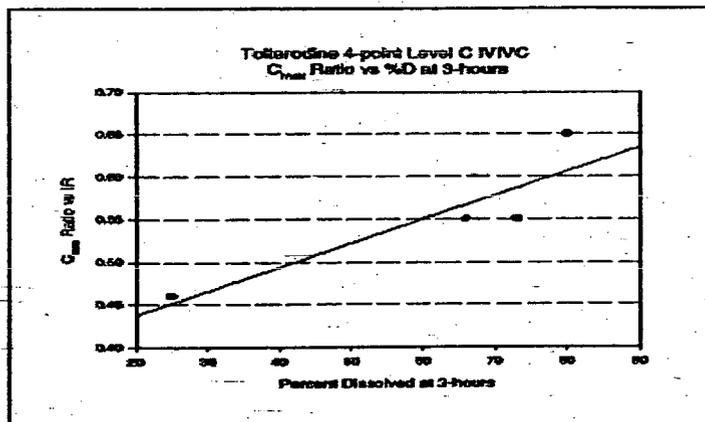
**Dissolution Specification**

**Method:** The drug-release method proposed for registration of tolterodine capsules utilizes the USP basket apparatus (Apparatus 1) at 100 rpm with 900 mL 0.05 M phosphate buffer at pH 6.8 and 37° C. The method employs a 10 mm) and a mobile phase consisting of 0.02 M phosphoric acid:acetonitrile (55:45). UV detection is employed at 254 nm and samples are quantitated versus external standards.

Time	Sponsor's Proposal	Reviewer's Comments
1 hour	—	Acceptable
3 hours	—	Acceptable
7 hours	—	Acceptable

**Rationale:** For all final formulations that were found to be bioequivalent for tolterodine, DD 01 (following single and multiple dose administration), the  $C_{max}$  ratios of extended release to IR was approximately in the range of 0.4 – 0.8. The following figure presented by the sponsor attempts to use the relationship of the  $C_{max}$  ratio (of the extended release formulation to the IR) against different dissolution scenarios (using formulations of different release rates) at the 3 hour time point. Based on this figure, above range of  $C_{max}$  ratio (0.4 – 0.8) and dissolution profiles provided in Attachment V, it may be concluded that theoretically, this dissolution specification will support the *in vivo* release of drug at levels that have been proven safe and effective.

Figure 11.9. Level C IVVC Based on Tolterodine  $C_{max}$  Ratio vs. the IR Tablet and Percent Dissolved at 3 Hours.



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**ANALYTICAL METHODOLOGY**

In order to analyze the serum levels of tolterodine and all its metabolites, two methods were used in general ( ). Both the methods are acceptable with based on sensitivity, precision and accuracy values. Please refer to Attachment VI for details of the methods and a summary of analytical results.

**Number of Pages**  
**Redacted** 8



Draft Labeling  
(not releasable)

**ATTACHMENT I**

**Title of study:** The effect of food on the bioavailability of tolterodine prolonged-release capsules. An open, randomized, cross-over trial in healthy volunteers.

**CTN:** 98-TOCR-010 **Document number:** c0003212

**Investigator:** \_\_\_\_\_

**Study center:** Pharmacia & Upjohn Clinical Research Unit, Kalamazoo, MI, USA

**Studied period:** FSI: August 17, 1998 LSO: September 3, 1998

**Phase of development:** I

**Objectives:** Primary: To show absence of a food effect on AUC, and to assess the effect of food on  $C_{max}$ , for tolterodine capsules. Secondary: To estimate the relative bioavailability ( $AUC_{\infty}$ ,  $C_{max}$ ) of the PR capsules (fasted) compared to the IR tablet (fasted). To estimate other pharmacokinetic parameters ( $AUC_{last}$ ,  $t_{lag}$ ,  $t_{max}$ ,  $t_{1/2}$ ) after single dose administration of tolterodine capsules, fed and fasted, and the immediate release tablet, fasted.

**Methodology:** An open, randomized, single-dose, 3-way cross-over, pharmacokinetic trial. The primary endpoints were the  $AUC_{\infty}$  and  $C_{max}$  ratios for the active moiety\* of the PR capsule fed relative to the PR capsule fasted. Other endpoints were: - Bioavailability (i.e., the  $AUC_{\infty}$  and  $C_{max}$  ratios for the active moiety) of the PR capsule (fasted) relative to the IR tablet (fasted); -  $AUC_{last}$  ratios based on the active moiety, for the PR capsule fed vs. fasted, and the PR capsule (fasted) vs. the IR tablet (fasted); -  $AUC_{\infty}$ ,  $AUC_{last}$  and  $C_{max}$  ratios based on concentrations of DD 01 and tolterodine, respectively, for the PR capsule fed vs. fasted, and the PR capsule (fasted) vs. the IR tablet (fasted); - Pharmacokinetic parameters ( $t_{lag}$ ,  $t_{max}$ ,  $t_{1/2}$ ) for the active moiety, DD 01 and tolterodine, respectively, for all treatments. Safety was evaluated by clinical chemistry, hematology and spontaneous AE reporting.

**Number of subjects (planned and analyzed):** 18 planned, 17 analyzed.

**Diagnosis and main criteria for inclusion:** Healthy volunteers.

**Test product, dose and mode of administration, batch number:** Tolterodine L-tartrate prolonged release 4 mg capsules, dosage 8 mg, orally, with and without food, batch no. 28,326.

**Duration of treatment:** Single doses.

**Reference therapy, dose and mode of administration, batch number:** Tolterodine L-tartrate 2 mg immediate release tablets, dosage 4 mg, orally, without food, batch no. OL,9608.

\* Active moiety = sum of unbound concentrations of tolterodine and DD 01

**Criteria for evaluation:**

**Pharmacokinetics:** At least complete serum concentration data for the two capsule-treatments, or complete data for the capsule vs. IR tablet comparison.

**Safety:** Administration of at least one dose of trial medication.

**Statistical methods:** Point estimates and 90% CIs for the AUC and  $C_{max}$  ratios. Other endpoints were presented descriptively.

\* Serum concentrations for the active moiety were calculated using serum concentration data for tolterodine and DD 01, and individual AGP data. The fraction unbound ( $f_u$ ) was calculated as follows:

$$f_u \text{ for tolterodine} = 1 / (1 + (2100 \times \text{AGP conc. (g/l)/42})) \quad (2)$$

$$f_u \text{ for DD 01} = 1 / (1 + (130 \times \text{AGP conc. (g/l)/42})) \quad (3)$$

The concentration of the active moiety = ( $f_{u \text{ tolterodine}} \times C_{\text{tolterodine}}$ ) + ( $f_{u \text{ DD 01}} \times C_{\text{DD 01}}$ ). Serum concentrations of tolterodine and DD 01 are reported as  $\mu\text{g/l}$ . For the active moiety this is converted to molar concentrations (nM). The molecular weight for tolterodine is 325.5 and for DD 01 341.5.

**ATTACHMENT II**

**Title of study:** Multiple dose pharmacokinetics and pharmacodynamics of tolterodine prolonged release capsules in comparison with tolterodine immediate release tablets. An open, randomized, cross-over trial in healthy volunteers.

**CTN: 97-TOCR-006 Document number: c0008272**

**Investigator:** \_\_\_\_\_

**Study center:** Pharmacia & Upjohn Clinical Research Unit, Kalamazoo, MI, USA.

**Studied period:** 1 February 1999 (FSI) to 30 April 1999 (LSO)

**Phase of development:** I

**Objectives:** The primary objective was to compare the steady-state pharmacokinetics ( $AUC_{24}$ ,  $C_{max}$  and  $C_{min}$ ) of tolterodine — capsules given once daily with those of tolterodine — tablets given twice daily. The secondary objectives were to

- assess other pharmacokinetic parameters for tolterodine and DD 01
- assess unbound serum concentrations, and pharmacokinetic parameters for the active moiety after multiple dosing of tolterodine — capsules and IR tablets
- assess pharmacokinetic parameters for the serum metabolites of tolterodine, other than DD 01, in the 4 poor and 4 of the extensive metabolizers, after multiple dosing of tolterodine — capsules and IR tablets
- assess basal salivation (change from baseline) after multiple dosing of tolterodine — capsules and IR tablets
- assess the safety and tolerability after multiple dosing of tolterodine — capsules and IR tablets

**Methodology:** Open, randomized, 2-way, multiple-dose, crossover, PK and PD.

The primary endpoints were the ratios for  $AUC_{24}$ ,  $C_{max}$  and  $C_{min}$ , respectively, between the PR capsules and the IR tablets for both tolterodine and DD 01. The secondary endpoints were:

- fluctuation index,  $t_{max}$ ,  $t_{1/2}$  for tolterodine and DD 01;
- $AUC_{24}$ ,  $C_{max}$ ,  $C_{min}$ , fluctuation index,  $t_{max}$ , apparent  $t_{1/2}$  for the active moiety;
- $AUC_{24}$ ,  $C_{max}$ ,  $C_{min}$ , fluctuation index,  $t_{max}$ ,  $t_{1/2}$  for the serum metabolites of tolterodine;
- area under the salivation curve (change from baseline;  $\Delta AUC_s$ ) during 12 hours post-dose, and maximum change in salivation from baseline ( $\Delta S_{max}$ ) during the 12-hour interval;
- ratios for the  $AUC_{24}$ ,  $C_{max}$ ,  $C_{min}$ ,  $\Delta AUC_s$  and  $\Delta S_{max}$  parameters described above;

Safety was evaluated by clinical chemistry, hematology and spontaneous AE reporting.

**Number of subjects (planned and analyzed):** 18 planned, 19 included, 17 analyzed.

**Test product, dose and mode of administration, lot number:** Tolterodine — 1 release capsules 4mg tolterodine L-tartrate, 1 capsule orally once daily, lot no. 28,446.

**Duration of treatment:** 6 days.

**Reference product, dose and mode of administration, lot number:** Tolterodine immediate release tablets ( — /Detrol) 2 mg tolterodine L-tartrate 1 tablet orally twice daily, lot no. 28,447.

**Criteria for evaluation:**

**Pharmacokinetics:** Complete serum concentration data after 6 days of treatment with each formulation.

**Statistical methods:** The primary endpoint (the bioavailability of the PR capsules relative to the IR tablets) was expressed as point estimates and 90% CIs. Ratios of  $C_{max}$  and  $C_{min}$  for the capsules relative to the tablet were analyzed in the same way, as were the pharmacodynamic parameters  $\Delta AUC_s$  and  $\Delta S_{max}$ . Other endpoints were presented descriptively.

**ATTACHMENT III**

**Title of study:** Dose-effect trial of tolterodine release capsules. A double-blind, double-dummy, cross-over trial in patients with overactive bladder.

**CTN:** 97-TOCR-002 **Document number:** c0003471

**Investigators:**

**Study centres:** Seven active centres in Finland (1), Norway (4), and Sweden (2).

**Publication (reference):** Not applicable

**Studied period:**

28 March 1998 - 13 July 1998

**Phase of development:** II

**Objectives:**

**Primary objective:** The primary objective was to estimate the dose of tolterodine that gives a pharmacodynamic effect equivalent to tolterodine IR tablets 2 mg b.i.d., using the dose-effect relationship at steady state (after 7 days of treatment) for mean residual urine volume measured over 12 hours.

**Secondary objectives:**

To study the dose-effect relationship of tol PR capsules compared with the effects of tol IR tablets 2 mg b.i.d for mean maximum urinary flow and mean salivation over 12 hours and mean volume voided per micturition, number of micturitions/24 hours, and number of incontinence episodes/24 hours, when measured over 72 hours.

To determine whether the steady state pharmacokinetics of tol PR (AUC<sub>t</sub> and C<sub>max</sub> for tolterodine and DD 01) are linear over the dose range of 2 to 8 mg.

To estimate the bioavailability of tol PR compared with that of tol IR tablets.

To study the safety and tolerability of various doses of tol PR as compared with tol IR tablets 2 mg b.i.d. and placebo, especially with respect to urinary retention and dry mouth.

**Methodology:** This was an international, multicenter, randomised, double-blind trial with a double-dummy, incomplete block, cross-over design consisting of three 1-week treatment periods and six treatments (2, 4, 6 and 8 mg tol PR, tol IR 2 mg b.i.d. and placebo). The trial was conducted in Finland, Norway, and Sweden.

**Number of patients (planned and analysed):** 60 patients were planned and 58 were included.

In total, 7 patient treatment periods were excluded from the per protocol analysis: Two due to patient's withdrawal (two patients) and 5 due to major protocol violations (three patients).

**Diagnosis and main criteria for inclusion:**

Male or female patient aged  $\geq 18$  years.

Body mass index (BMI) between 18 and 29 kg/m<sup>2</sup> (protocol amendment 3).

Urinary urgency present.

Symptoms of overactive bladder present for  $\geq 6$  months.

Mean volume voided per micturition of  $\leq 200$  ml, as confirmed by the micturition chart during the run-in period.

Symptoms of urinary frequency ( $\geq 8$  micturitions, on average, per 24 hours) and/or symptoms of urge incontinence ( $\geq 1$  incontinence episode, on average, per 24 hours), as confirmed by the micturition chart during the run-in period.

**Test product, dose and mode of administration, batch number:** Two different strengths (2 and 4 mg) of tol PR capsules were given in combinations to provide daily doses of 2, 4, 6 and 8 mg. Batch numbers: A049712 (2 mg), A059712 (4 mg), A029803 (2 mg) and A039803 (4 mg).

**Duration of treatment:** 7 days on each treatment.

**Reference therapy, dose and mode of administration, batch number:** Tolterodine IR tablets 2 mg b.i.d. batch number: 6401. Placebo tablets and capsules batch numbers: A019404 (placebo tablets), A079712 (2 mg placebo capsules) and A089712 (4 mg placebo capsules).

**Criteria for evaluation:**

**Efficacy:** All patients who adhered reasonably well to the protocol for a given treatment were included in the per protocol population for that treatment. Thus, it was possible for a patient to be included in the per protocol population for one treatment but not for another.

**Safety:** All patients who received at least one dose were included in the safety population.

**Statistical methods:** The primary objective was to estimate the dose of tolterodine — that gives a pharmacodynamic effect equivalent to tol IR tablets 2 mg b.i.d., using the dose-effect relationship at steady state (after 7 days of treatment) for mean residual urine volume measured over 12 hours. The idea was to model the mean effect as a linear function of the log-transformed doses (the covariate). An analysis-of-covariance model with patient, period and formulation (tol PR capsule, tol IR tablet, or placebo) as fixed factors and  $\ln(\text{dose})$  as a covariate was used.

More precisely, let  $Y_{ijk}$  be the mean residual volume of the  $i^{\text{th}}$  patient in the  $j^{\text{th}}$  period and the  $m(k)^{\text{th}}$  formulation. Then

$$Y_{ijk} = \text{overall mean} + \text{patient}_i + \text{period}_j + \text{formulation}_{m(k)} + \beta * \ln(\text{dose})_{ijk} + \text{error}_{ijk}$$

Where

$\beta$  = the slope of the straight line associating  $\ln(\text{dose})$  and mean effect

$i = 1, 2, \dots, 60$  (the patients)

$j = 1, 2, 3$  (the period)

$m(k) = 1$  when  $k = 1$  (placebo),

$m(k) = 2$  when  $k = 2, 3, 4, 5$  (2, 4, 6 and 8 mg tol PR )

$m(k) = 3$  when  $k = 6$  (tol IR 2 mg b.i.d.)

The  $\ln(\text{dose}) = 0$  was used for placebo and tol IR 2 mg b.i.d. However, this choice did not effect the results of the analysis since the estimate of beta was only influenced by formulations with more than one dose.

With  $F_n$ ,  $F_o$  and  $\beta$  denoting the estimated effects for the new formulation (tol PR), the old formulation (tol IR tablet) and the covariate, the equivalent dose could be estimated as  $D = \exp((F_o - F_n)/\beta)$ . The 95% confidence limits for  $D$  were calculated by using Fieller's method on  $\ln(D)$  and then exponentiating the limits.

The following variables were analysed in the same way as the primary efficacy variable:

Mean volume voided (ml) per micturition, measured over 72 hours

Mean maximum urinary flow (ml/s) per micturition, measured over 12 hours

Number of micturitions per 24 hours, measured over 72 hours

Number of incontinence episodes per 24 hours, measured over 72 hours

Mean salivation (g/min), measured over 12 hours

The same model was also used to assess the linearity of the pharmacokinetic parameters for tol PR over the dose interval. In order to study the relative bioavailability of tol PR 4 mg compared with tol IR 2 mg b.i.d., estimates of the mean ratio (test/reference) together with the corresponding 90% confidence limits are presented. The rationale for the 90% confidence interval is that the estimated interval can be compared to the standard BE interval (i.e. 0.8 - 1.25).

**ATTACHMENT IV**

[Amendment 9 to NDA 21-228, sent by sponsor on 10/30/2000]

**Tolterodine -Release Capsules:  
 Question from FDA Biopharmaceutics Reviewer  
 (I2000-132)**

*Provide written confirmation that the formulation of extended release tolterodine used in the clinical trials is exactly the same as the to be marketed formulation.*

The  formulation used in the primary safety/efficacy study (protocol 98-TOCR-007) is identical to the formulation intended for the market. The finished capsules differ only in color: yellow capsules were used in the clinical study, while blue (4 mg) and blue-green (2 mg) capsules will be used for the marketed product.

Other formulations were explored during the clinical program. All formulations are fully described in section 8, "Investigational Formulations", of the CMC Summary and are cross-referenced to the clinical study in which they were used.

Table 11.17. Formulation P902255A01†:  
 Tolterodine tartrate  Release Capsules, 4 mg  
 (contains )

Amount per 4 mg Capsule (mg)	Component
	Hydroxypropyl methylcellulose
	Hydroxypropyl methylcellulose
	<b>TOTAL</b>
	Hard Gelatin Capsule

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† Final formulation

ATTACHMENT V

Drug-Release Data for Tolterodine tartrate -- Capsules, 4 mg.  
 Lot No. 9806084-Z15 (N=12).

Time (Hours)	Percent Released				Individual Capsule Data
	High	Low	Average	RSD	
1			14	10.3	
2			36	4.7	
3			61	4.2	
5			85	3.0	
7			93	3.4	
9			95	2.8	
15			98	2.6	

Registration Test Method, Date: 10Jul98, 21Jul98

Drug-Release Data for Tolterodine tartrate -- Capsules, 4 mg.  
 Lot No. 9807665-Z17 (N=12).

Time (Hours)	Percent Released				Individual Capsule Data
	High	Low	Average	RSD	
1			15	6.3	
2			39	5.3	
3			66	5.3	
5			87	4.3	
7			95	5.3	
9			96	2.5	
15			98	3.3	

Registration Test Method, Date: 22Sep98

Time (Hours)	Percent Released				Individual Capsule Data
	High	Low	Average	RSD	
1			15	9.5	
2			38	9.3	
3			63	6.6	
5			88	3.5	
7			93	3.6	
9			95	3.5	
15			98	2.5	

Registration Test Method, Date: 24Sep98

**Drug-Release Data for Tolterodine tartrate — Capsules, 4 mg.  
 Lot No. 9807680-Z19 (N=12).**

**ATTACHMENT VI**

Table 18.1. Analytical Method Summary for Quantitation of Tolterodine and DD 01 (5-hydroxymethyl metabolite).

Protocol No.	Biological Fluid	Method Description	Specificity	Sensitivity Range	Ref. No.
97-TOCR-001 97-TOCR-002 97-TOCR-003 98-TOCR-005 98-TOCR-010	Serum	Method / Tolterodine and DD 01 determined with G <sup>+</sup>	Tolterodine; DD 01	1	0

Table 18.2. Analytical Method Summary for Quantitation of Tolterodine and Five Metabolites.

Protocol No.	Biological Fluid	Method Description	Specificity*	Sensitivity Range	Ref. No.
98-TOCR-008	Serum		Tolterodine; DD 01; Ib; IIB; IVa; IVb	1 or 1	31

\* Ib = desalkylated tolterodine; IIB = desalkylated hydroxylated tolterodine; IVa = carboxylated tolterodine; IVb = desalkylated carboxylated tolterodine

Table 10.3 Analytical Summaries of Tolterodine and the Metabolites in Human Serum for Clinical Pharmacokinetic Studies.

Protocol no.	Analyte*	Range (ng/mL)	Cal Std Accuracy (%)	Cal Std Precision (%)	QC Accuracy (%)	QC Precision (%)	Method	Ref. no.
97-TOCR-001	Tolterodine DD 01						A	33
97-TOCR-002	Tolterodine DD 01						A	34
97-TOCR-003	Tolterodine DD 01						A	35
98-TOCR-005	Tolterodine; DD 01						A	0
98-TOCR-008	Tolterodine; DD 01; Ib; IIB; IVa; IVb						B	37
98-TOCR-010	Tolterodine DD 01						A	38

\* Ib = desalkylated tolterodine; IIB = desalkylated hydroxylated tolterodine; IVa = carboxylated tolterodine;

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