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.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0226

Reviewer's Comments:

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

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0227

Study Number: 92-OATA 001

Study Title: Electrophysiological heart effects of repeated iv. Atropine injections, repeated oral dosage of tolterodine and placebo to healthy human volunteers in a parallel group design (study B)

Study Objectives: The study was designed to discover potential electrophysiological heart effects of tolterodine at two different doses in healthy human volunteers. A comparison was made to treatment with placebo and treatment with atropine.

As a secondary objective a pharmacokinetic evaluation of tolterodine was performed.

Study design: The study was single-blind, placebo controlled and with three parallel arms. It was randomized for 36 subjects, 12 in each of the three groups. The three groups received the following sequences of drug:

Table 38.

Group	Atropine day	Wash-out	7 days of tablets	Follow up
A	5 saline injections	3-7 days	Placebo tablets b.i.d.	2 days
B	5 atropine injections	3-7 days	tolterodine, 2 mg b.i.d.	2 days
C	5 atropine injections	3-7 days	tolterodine, 4 mg b.i.d.	2 days

Subjects: The study was designed for 36 healthy volunteers, 12 in each of the three groups. The choice of sample size was based on power considerations and on results from previous studies of utilizing determination of QT_c-prolongation in healthy subjects.

Phenotyping for Cytochrome P-450 2D6 (Debrisoquine) and 2C19 (Mephenytoin) was performed prior to the study and the result was used in the inclusion/exclusion process. The procedure was as follows:

After emptying the bladder at bedtime, each subject took one tablet of Mephenytoin (100 mg) and 1/2 a tablet Debrisoquine (10 mg) orally. Urine was collected over night and the concentration relation (metabolic ratio, MR) between Debrisoquine and 4-OH-Debrisoquine as well as the concentration relation between the enantiomers of mephenytoin (enantiomeric ratio, S/R) were determined by

A subject with a metabolic ratio of more than 12.2 for Debrisoquine / 4-OH-Debrisoquine and/or a S/R enantiomeric ratio of mephenytoin of approximately 1 were considered as a poor metabolizer.
The analysis of urine for phenotyping as described (above) was performed at

Dosage Forms, Dosage and Administration:
tolterodine table. 2 mg Pharmacia AB). Batch no 3022-0-A1
Placebo (tolterodine) table. Pharmacia AB). Batch no DFP 344
Atropine sulph. inj. sol., 0.5 mg/ml Pharmacia AB), Batch no SG 090A.
Sodium chloride, sterile solution 9 mg/ml. Pharmacia AB), Batch no 3011222.
Debrisoquine tablet, 20 mg (for phenotyping). Batch no 1180.
Mephenytoin tablet, 100 mg (for phenotyping). Batch no 361 F3576.

Saline injections:
I.v. injection of 5 ml saline during 1 minute with a subsequent catheter flush with 5 ml saline. The procedure was repeated 5 times with half an hour intervals.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0228

Atropine day:
I.v. injection of 1 ml atropine (0.5 mg/ml) in 4 ml saline during 1 minute with a subsequent catheter flush with 5 ml saline. The procedure was repeated 5 times with half an hour intervals. Five doses of atropine were a maximum and it was optional to give fewer injections at the discretion of the investigator.

tolterodine /placebo day 1- 7:
The subjects received tolterodine, 2 mg b.i.d. (one active and one placebo tablet), 4 mg b.i.d. (two active tablets) or 2 placebo tablets b.i.d. during 7 consecutive days. At day 7 the tablets were given in the morning only.

The tablets were intended to be taken in the morning (8 am) and evening (8 pm) and were to be swallowed with half a glass of water. The exact time was to be recorded on a special form by the subjects.

Blood sampling: Blood samples (7 ml) for determination tolterodine in serum was drawn by means of an intravenous catheter as follows:
Day 1: Prior to first dose (baseline) and 0.5, 1, 1.5, 2, 3.5, 5, 7, 9 and 12 hours thereafter.
Day 4: Prior to morning dose and 1 and 5 hours after morning dose.
Day 7: Prior to morning dose and 0.5, 1, 1.5, 2, 3.5, 5, 7, 9 and 12 hours thereafter.
Day 8: 24 hours after last dose
Day 9: 48 hours after last dose

Analytical methodology:

RESULTS

ECG-variables

Atropine treatment
During atropine/placebo treatment there were statistically significant differences between treatments for the ECG- variables HR, QT, QT_c, TDUR and T-wave amplitude (positive deflection, +Tampl in leads I-III, aVF, V_1-V_6 and negative deflection, -Tampl in leads aVR and V_1) as regards mean changes from baseline.

For the other ECG-variables investigated in this study (PDUR, PR, QRS and T-wave amplitude - positive and negative - in other leads than those mentioned above) no more than occasional statistically significant differences could be shown, although there were tendencies to a decrease in mean value for several of these variables.

The differences between placebo and atropine are fully expected. The increase in HR which is a result of the parasympathetic inhibition by atropine is logically followed by a shortening of several individual ECG parameters. The manual evaluation of T wave morphology in V_{1-6} after atropine did not reveal any change in this parameter.

Tolterodine treatment
During tolterodine /placebo treatment statistically significant differences between treatments as regards mean changes from baseline could be seen only on a few isolated occasions in time.
HR was not influenced by 2 mg dosage level. With 4 mg, however, in less than half of the measurements, there was a statistically significant increase (range; 7-13 beats/min., i.e. < 20%). These increases

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0229

occurred clustered to the first hours after the morning dose, i.e. around time for C_{max} This finding was fully expected due to the anticholinergic nature of the drug.
The manual evaluation of T-wave morphology in lead V_{1-6} did not reveal any change in this parameter after administration of tolterodine.

No evidence of any increase in QT or QT_c after administration of tolterodine were seen, neither when looking at the group mean values nor when looking at the individual extreme values.
Minimum and maximum group mean values of QT and QT_c during the atropine day and during tolterodine day 1 and 7 are shown in Table 39.

Table 39. Minimum and maximum group mean values and (SD) of QT and QTc during the atropine day and during tolterodine day 1 and 7.

QT (ms)		Placebo group	tolterodine 2 mg b.i.d.	tolterodine 4 mg b.i.d.	Atropine
Baseline*		420 (29)	429 (27)	419 (17)	410 (18)
Day 1	maximum				
	minimum				
Day 7	maximum				
	minimum				
QTc (ms)		**Placebo group**	**tolterodine 2 mg b.i.d.**	**tolterodine 4 mg b.i.d.**	**Atropine**
Baseline*		421 (21)	425 (19)	415 (13)	410 (15)
Day 1	maximum				
	minimum				
Day 7	maximum				
	minimum				

- 2nd baseline measurement

The normal QT_c is often stated to be below 440 ms. Recent literature have however shown that the normal variability of QT and QT_c is substantially higher than previously anticipated. Normal ranges of QT_c of up to 506 ms and of QT up to 487 have been reported. Furthermore, for individual subjects a high degree of daily variability in QT_c has been shown.

For comparison, the minimum and maximum extreme values obtained during baseline measurement, during day 1 and during day 7, for the different groups in this study are presented in Table 40. Individual values of a $QT_c > 440$ were frequently seen also in our material.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0230

Table 40. Minimum and maximum extreme values of QT and QT_c during the atropine day and during tolterodine day 1 and 7.

QT (ms)		Placebo group	tolterodine 2 mg b.i.d.	tolterodine 4 mg b.i.d.	Atropine
Baseline*	maximum minimum				
Day 1	maximum minimum				
Day 7	maximum minimum				
QTc (ms)		**Placebo group**	**tolterodine 2 mg b.i.d**	**tolterodine 4 mg b.i.d**	**Atropine**
Baseline*	maximum minimum				
Day 1	maximum minimum				
Day 7	maximum minimum				

* 2nd baseline measurement

Blood pressure

Atropine treatment

During atropine/placebo treatment there were statistically significant differences between treatments for diastolic blood pressure but not for systolic blood pressure as regards mean changes from baseline. Here, baseline was defined as the mean of the two replicate BP measurements recorded immediately before the first iv. injection. These significant differences were present between 1 hour 15 min (after 3rd dose) and 2 hours 15 min. (after the 5th dose). For diastolic blood pressure there was an estimated average difference between atropine treated subjects and placebo treated subjects of about +10% (of baseline). An increase in diastolic blood pressure was expected, but its magnitude (6.1 - 8.9 mm Hg as a range) was somewhat higher than anticipated.

Tolterodine treatment

During tolterodine/placebo treatment there were no statistically significant differences between treatments; neither for diastolic nor for systolic blood pressure as regards mean changes from baseline other than on a few isolated occasions in time.

The baseline was defined as the mean of the two replicate measurements recorded immediately before the first tablet intake on day 1 of tolterodine/placebo treatment.

Serious adverse events: No serious adverse events occurred during the trial.

Pharmacokinetics: Mean pharmacokinetic parameters of tolterodine and the 5-Hydroxymetabolite (5-HM) are presented in Table 41, below.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0231

Table 41. Mean (SD) Pharmacokinetic Parameters of tolterodine and 5-Hydroxymetabolite (n=II).

	Tolterodine				5 - H M			
Dose, bid	**Cmax, (µg/l)**	**tmax, (h)**	**AUC*, (µg - h/l)**	**t½,z, (h)**	**Cmax, (µg/l)**	**tmax, (h)**	**AUC*, (µg - h/l)**	**t½,z, (h)**
2 mg, ** day 1	2.2 (2.1)	2.0 (0.9)	12.1 (15.1)	2.4 (0.7)	2.1 (0.6)	2.0 (0.8)	12.2 (4.3)	3.2 (1.5)
2 mg, ** day 7	2.5 (2.3)	2.5 (1.1)	11.8 (14.2)	2.4 (0.9)	2.2 (0.7)	2.5 (1.0)	12.1 (3.3)	3.4 (1.7)
4 mg, day 1	4.2 (5.2)	2.2 (0.9)	22.4 (33.8)	2.5 (0.7)	4.2 (1.4)	2.5 (1.2)	25.0 (9.8)	3.3 (1.2)
4 mg, day 7	4.6 (6.1)	2.6 (1.0)	23.0 (34.1)	2.2 (0.5)	4.4 (1.2)	2.8 (1.3)	25.5 (7.3)	3.2 (0.8)

* The AUC values are presented as AUC_0^{∞} after single-dose administration and AUC_0^{12} after multiple dose administration.

** Note that subject no 29 received only atropine and is not included in this table.

No accumulation of tolterodine or its metabolite 5-HM was seen after multiple-dose administration. C_{max} and AUC increased proportionally with increasing dose, suggesting linearity of pharmacokinetics. Tolterodine and 5-HM were present within the same concentration range.

Sponsor's Conclusions:

- Intermittent intravenous administration of atropine in doses of 0.5 mg significantly depressed T-amplitude and shortened the T-duration, QT and QTc between cumulative doses of 1 - 2.5 mg.
- Tolterodine, 2 and 4 mg b.i.d. did not prolong QT or QT_c.
- Tolterodine, 2 and 4 mg b.i.d. did not influence either T-wave amplitude, T-wave duration or T-wave morphology.
- Tolterodine, 2 and 4 mg b.i.d. has not created any kind of safety concern; neither regarding cardiovascular evaluation, clinical chemistry, hematology, urinalysis nor adverse events.
- No accumulation of tolterodine or its 5-hydroxymetabolite was seen after multiple dose administration.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0232

Study Number: 93-OATA 004

Study Title: Pharmacological effects are kinetics of tolterodine in poor and extensive metabolizers of debrisoquine.

Study Objectives: To investigate the pharmacological effects and kinetics of tolterodine in poor and extensive metabolizers of debrisoquine.

Study design: This was an open, comparative, multiple dose study.

Subjects: 16 healthy male volunteers were enrolled

Phenotyping for Cytochrome P-450 2D6 (Debrisoquine) and 2C19 (Mephenytoin) was performed prior to the study and the result was used in the inclusion/exclusion process. The procedure was as follows:

After emptying the bladder at bedtime, each subject took one tablet of Mephenytoin (100 mg) and 1/2 a tablet Debrisoquine (10 mg) orally. Urine was collected over night and the concentration relation (metabolic ratio, MR) between Debrisoquine and 4-OH-Debrisoquine as well as the concentration relation between the enantiomers of mephenytoin (enantiomeric ratio, S/R) were determined by

A subject with a metabolic ratio of more than 12.2 for Debrisoquine / 4-OH-Debrisoquine and/or a S/R enantiomeric ratio of mephenytoin of approximately 1 were considered as a poor metabolizer.
The analysis of urine for phenotyping as described (above) was performed at

Test Product: Tolterodine, 2 mg tablets, batch No. 3022-O-A-1.

Treatment Duration: 4 mg b.i.d. for 8 days.

Results:
The pharmacokinetic parameters of tolterodine from poor and extensive metabolizers are included in Table 42.

Table 42.

	F (%)	Cmin (µg/l)	Cmax (µg/l)	Cl (l/h)	t½ (h)
EM	17±9.5	0.38±0.09	5.1±5.6	45±12	2.2±0.37
PM	65±26	15±6.0	38±15	9.5±1.8	9.6±1.5

Sponsor's Conclusions:

- Tolterodine L-tartrate 4 mg b.i.d. and 1.8 mg infusion has not created any kind of safety concern; neither regarding cardiovascular evaluation, clinical chemistry, hematology, urinalysis, nor adverse events.
- Tolterodine is highly and selectively metabolized by CYP2D6 to DD01.
- It seems that the higher tolterodine concentrations in the poor metabolizers compensate for the absence of the active metabolite DD01 in these subjects.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0233

Study Number: CTN 93-OATA-007

Study Title: Tolerability and pharmacokinetic effects of tolterodine L-tartrate in elderly. A randomized double-blind study in healthy volunteers.

Objectives: To investigate safety and tolerability of tolterodine in elderly with special reference to cardiovascular effects. To investigate the pharmacokinetics after single- (1, 2 and 4 mg) and multiple-dose (2 mg b.i.d.) administration.

Study Design: Randomised double-blind parallel group design (4 groups).

Subjects : 8 male and 18 female healthy elderly volunteers (age 64-80 years) were enrolled in the study. Two (2) subjects, (poor metabolizers) were treated separately and received the doses unblinded.

Test product: Tolterodine L-tartrate tablets, 1 mg (Pharmacia AB). Batch No: B039303
Composition

Active ingredient:			
Tolterodine L-tartrate	mg		
Other ingredients:		Tablets coated with:	
Cellulose microcrystalline	mg	Eudragit E 100	mg
Calciumhydrogen phosphate	mg	Titaniumdioxide	mg
Sodium starch glycolate	mg	Talc	mg
Magnesium stearate	mg	Magnesium stearate	mg
Silica anhydrous	mg	Polyethylene glycole	mg
		Vanillin	mg

Reference product: Placebo (Pharmacia AB). Batch No: B019303
Composition

Ingredients:		Tablets coated with:	
Cellulose microcrystalline	mg	Eudragit E 100	mg
Calciumhydrogen phosphate	mg	Titaniumdioxide	mg
Magnesium stearate	mg	Talc	mg
Silica anhydrous	mg	Magnesium stearate	mg
		Polyethylene glycole	mg
		Vanillin	mg

Duration of treatment: 1, 2, and 4 mg single-dose administration and 2 mg b.i.d. for 5 days.

Blood and Urine Sampling:
Single dose administration: Venous blood samples were drawn before administration of study drug and at 15, 30, 45 minutes and at 1, 1.5, 2, 4, 6, 8, 10, 12, 24 and 25 hours after drug administration.

Multiple dose administration: Venous blood samples were drawn immediately before administration on day 4, before administration of study drug on day 5 and at the following times after administration on day 5: 15, 30, 45 minutes, 1, 1.5, 2, 4, 6, 8, 10, 12, 24 and 25 hours.

Urine: A urine sample was collected immediately before dosing on day one (single dose part). Urine was collected quantitatively in the intervals 0-12 and 12-24 hours during single dosing and on day five during multiple dosing. Each urine sample was carefully shaken and a 10 ml aliquot was prepared. The samples were frozen and stored at -20 °C until analyzed for unchanged drug and DD 01.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0234

Analytical Methodology:

Serum protein binding:
The degree of in vivo binding to serum proteins was estimated for tolterodine and DD 01. The free concentration (Cu) and total serum concentration (Cs) were measured in the 1 hour serum sample after the last dose (day five, multiple dose session). Free fraction (fu) was to be estimated from the ratio of Cu to Cs. Free concentration, Cu, in serum was to be measured by means of equilibrium dialysis.

RESULTS
Safety: No treatment related effects on clinical laboratory safety variables were seen comparing screening to post-study assessment. No clinically significant findings were seen considering changes in QTc, or in the other measured ECG parameters .

Pharmacokinetics: A summary of the pharmacokinetic parameters is presented below.

Table 43. Mean (SD) Pharmacokinetic Parameters of Tolterodine and DD 01 after multiple dose (5 days) administration of 2 mg b.i.d. tolterodine L-tartrate

Analyte	tmax (h)	Cmax (µg/l)	Cav (µg/l)	$t_{1/2}$ (h)	AUC0-t (µgh/l)	CL_O (l/h)	fe (% of dose)
tolterodine	0.9 (0.28)	1.6 (0.95)	0.52 (0.37)	2.8 (0.69)	6.2 (4.4)	343 (239)	<1.0
DD 01	1.0 (0.24)	2.7 (0.66)	1.0 (0.34)	3.6 (0.67)	12 (4)	----	14 (4.8)

Table 44. Mean (SD) Pharmacokinetic Parameters of Tolterodine and DD 01 after single oral administration of tolterodine L-tartrate.

	tolterodine						DD 01				
Dose (mg)	tmax (h)	Cmax (µg/l)	Cav (µg/l)	$t_{1/2}$ (h)	AUC 0-t (µgh/l)	CL_O (l/h)	tmax (h)	Cmax (µg/l)	Cav (µg/l)	$t_{1/2}$ (h)	AUC 0-t (µgh/l)
1	0.83	0.78	0.22	2.4	2.6	372	0.88	1.1	0.47	3.9	5.7
(n=6)	(0.20)	(0.46)	(0.13)	(1.2)	(1.6)	(235)	(0.14)	(0.39)	(0.16)	(1.1)	(2.0)
2	0.72	1.6	0.36	1.9	4.4	353	0.83	2.5	0.92	2.9	11
(n=6)	(0.20)	(0.55)	(0.12)	(0.68)	(1.4)	(151)	(0.38)	(0.73)	(0.31)	(0.2)	(3.7)
4	0.63	3.8	1.2	2.8	14	399	0.71	5.0	2.1	3.6	25
(n=6)	(0.14)	(3.2)	(1.0)	(0.48)	(12)	(330)	(0.19)	(2.1)	(1.0)	(0.72)	(12)

Poor metabolizers
The poor metabolizers showed no detectable concentrations of DD 01. The half-life of tolterodine was 3-4 times longer than in extensive metabolizers, Table 45.

Table 45. Pharmacokinetic parameters of tolterodine in Poor Metabolizers (P-450 2D6).

Subject No.	Dose (mg)	tmax (h)	Cmax (µg/l)	Cavg (µg/l)	$t_{1/2}$ (h)	AUC* (µgh/l)	Cl_O (l/h)	f_e (% of dose)
	2	0.75	7.4	8.9	11	108	13	n.a.
	2	1.5	12	18	15	214	6.4	n.a.
	2 bid	2.0	25	18	16	215	6.4	8.4

The single-dose pharmacokinetics suggests dose proportionality. The steady-state maximum concentrations of tolterodine and DD 01 were 1.6 and 2.7 µg/l, respectively and the respective, half-lives were 2.8 and 3.6 hours. No accumulation of tolterodine or DD 01 was seen after b.i.d. multiple dose administration with the exception of the poor metabolizer. This subject had a two-fold accumulation, which is in accordance with the longer half-life (16 hours).

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0235

Steady-state serum concentration-time profiles of tolterodine and DD 01 after multiple doses of tolterodine (2 mg b.i.d.) are depicted in Figures 6 and 7.

Figure 6. Serum Concentration versus Time Profile of Tolterodine

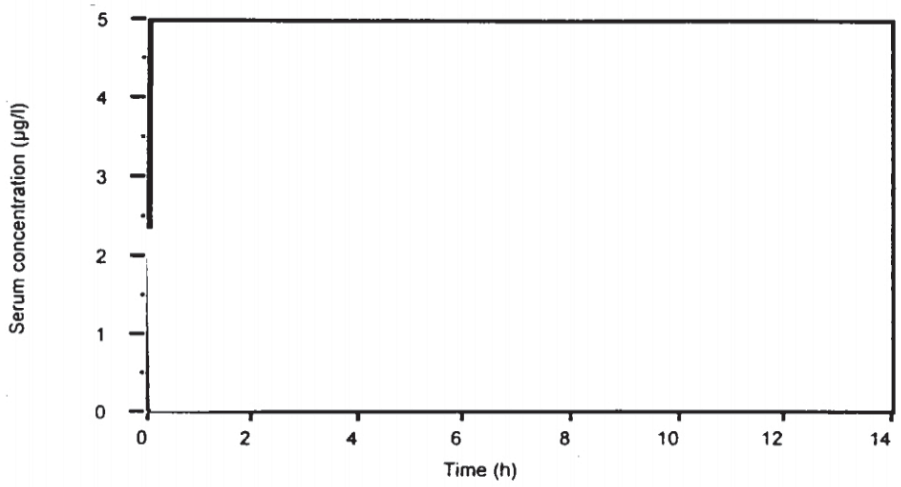
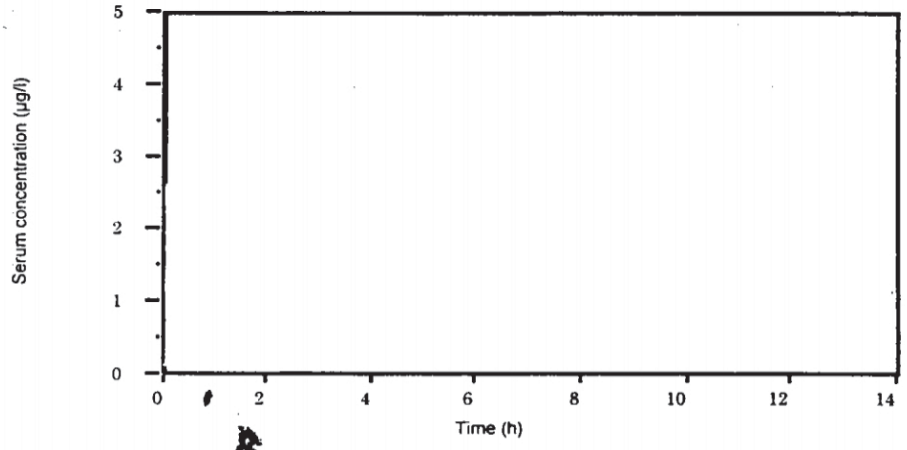


Figure 7. Serum Concentration versus Time Profile of DD01.



Sponsor's Conclusions:

- From the present study with elderly subjects it can be concluded that tolterodine 1, 2 and 4 mg given as single doses and 2 mg b.i.d did not create any kind of safety concerns; neither regarding cardiovascular effects (ECG, heart rate and blood pressure), clinical chemistry, hematology, urinalysis nor adverse events.

- The single-dose pharmacokinetics suggests dose proportionality with respect to C_{max} and AUC.

- No accumulation of tolterodine or DD 01 was seen after multiple dose with exception for the poor metabolizer. This subject had a two-fold accumulation, which is in accordance with the longer half-life in this subject.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0236

- C_{avg} , C_{max} and AUC of tolterodine and DD 01 increased proportionally with increasing dose and time. There were no consistent dose-dependent changes in half-life of tolterodine or DD 01 or oral clearance of tolterodine.

- The serum concentration levels of DD 01 was about the same or a little higher than those of tolterodine. No accumulation of either tolterodine or DD 01 was seen after multiple-dose administration.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0237

Study Number: CTN: 94-OATA-013

Study Title: Safety and tolerability of tolterodine after multiple-dose administration to elderly subjects: A randomized, double-blind, placebo-controlled study

Objectives: The primary objective was to assess the safety and tolerability of multiple doses of tolterodine in elderly subjects at least 70 years of age. A secondary objective was to determine the serum concentrations of both tolterodine and DD 01, and a final objective was to assess the feasibility of administration of micturation charts in this age group.

Study Design: This was a multi-center, randomized, double-blind, parallel, three groups, placebo controlled study.

Subjects: Thirty three elderly subjects 70 years of age or older; at least 50% >75 years were enrolled in the study. The subjects were randomized, 7 to the placebo and 26 to the active treatment (14 - 1 mg and 12 - 2 mg) groups. Four subjects (12%) were phenotype for CYP2D6 as poor metabolizers according to the dextro-methorphan assay.

Test product: Tolterodine L-tartrate tablets (0.5 and 1 mg) batch No. BB121027 and B039303, respectively

Duration & Dosage: The subjects received either placebo, or tolterodine 1 or 2 mg b.i.d. for 28 consecutive days.

Assay Methodology:

Blood Sampling: Venous blood samples (5 mL Vacutainer® tube, no additives) for assessment of serum drug / metabolite levels were collected pre- and post-morning dose at 0, 0.5, 1, 2, 4, 6 and 8 hr on Days 1 and 28. On Day 7, four blood samples were obtained at 0, 0.5, 1 and 2 hours post-morning dose.

Results

Kinetics after a Single Dose (Day 1)

Absorption of tolterodine was rapid with the T_{max} attained following both doses between 0.5 to 2 hours. For the 1 and the 2 mg doses respectively, the single dose estimates (mean ± SD) of tolterodine were: C_{max} 2.8 (±2.8) and 2.8 (±2.1) ng/mL, $AUC_{0-\infty}$ 7.09 (±4.75) and 8.76 (±6.09) ng.hr/mL, the terminal half-life ($t_{1/2},\lambda_z$) 2.06 (±0.68) and 2.16 (±0.44) hr. Body weight normalized estimates of CL_o were 2.18 (±1.43) and 3.02 (±1.64) L/hr/kg, and for V_d,λ_z were 6.2 (±4.30) and 9.0 (±4.7) L/kg following the 1 and 2 mg doses, respectively.

Except for C_{max}, no statistically significant differences between the 1 and 2 mg doses were seen in the dose-normalized tolterodine estimates: $AUC_{0-\infty}$ ($p = 0.218$), CL_o ($p = 0.660$) or V_d ($p = 0.761$) following single doses. Both T_{max} and $t_{1/2},\lambda_z$ were independent of the dose.

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For DD 01, the estimates of T_{max} and C_{max} (mean ± SD) were 0.9 (±0.4), 0.8 (±0.3) hr and 2.0 (±1.4) and 3.5 (±1.6) ng/mL following the 1 and 2 mg tolterodine doses, respectively. The $AUC_{0-\infty}$ (mean ± SD) for those respective doses were 10.7 (±7.41) and 16 (±8.05) ng.hr/mL. Terminal $t_{1/2},\lambda_z$ for DD 01 was about 3.57 (±1.41) and 2.89 (±0.37) hr following the 1 and 2 mg tolterodine doses, respectively. Except for $t_{1/2},\lambda_z$, no statistically significant differences between the 1 and 2 mg single doses were seen in the dose-normalized DD 01 parameters C_{max} ($p = 0.155$) or $AUC_{0-\infty}$ ($p = 0.094$). Overall, the DD 01 elimination profile was similar to tolterodine.

In poor metabolizers (n = 4), tolterodine C_{max} ranged from ng/mL and was attained in ~1 hr. Consistent with the magnitude of the dextromethorphan phenotype estimate, the corresponding $AUC_{0-\infty}$ ranged from ng.hr/mL and the CL_o from L/hr/kg. Although the kinetic parameters obtained from PMs were not compared statistically to those obtained from EMs, it is apparent that relatively higher values of C_{max}, $AUC_{0-\infty}$ and $t_{1/2},\lambda_z$ for tolterodine were observed.

Kinetics after Repeat Dosing (Day 28): Steady-State

Given the short half-life of tolterodine, its steady state was easily achieved by Day 28. The steady-state estimates (mean ± SD) of C_{max} were 2.4 (±1.6) and 4.1 (±3.8) ng/mL, and were attained within 1 hr (T_{max}) post-1 and 2 mg doses (b.i.d regimen), respectively. For these two doses, the estimates of AUC_{0-12} were 8.59 (± 4.87) and 13.5 (±9.38) ng.hr/mL. The $t_{1/2},\lambda_z$ was about 2 hr for both dose levels, hence independent of dose. Weight normalized oral clearance (CL_o) at steady-state was 1.94 (±1.69) and 2.61 (±2.42) L/hr/kg, while estimates of V_d,λ_z were 5.69 (±5.41) and 7.5 (±5.9) L/kg following twice daily regimen of 1 and 2 mg doses, respectively, for 28 days.

No statistically significant differences were apparent between the 1 and 2 mg dose levels in the dose-normalized estimates for tolterodine C_{max} ($p = 0.647$), AUC_{0-12} ($p = 0.909$), CL_o ($p = 0.298$) or V_d ($p = 0.796$). T_{max} ($p = 0.867$) and $t_{1/2},\lambda_z$ ($p = 0.713$) were unaltered. Lack of dose effect on kinetic parameters suggested dose-independent kinetics for the two dose levels.

At steady state, the peak metabolite concentrations following both doses were similar to the C_{max} of the parent drug. The estimates (mean ± SD) of C_{max} were 2.5 (±1.5) and 3.9 (±2.2) ng/mL, which were attained at about 1 hr (T_{max}) following the 1 and 2 mg tolterodine doses, respectively. The corresponding estimates of AUC_{0-12} were 10.60 (± 4.74) and 18.30 (±9.07) ng.hr/mL, and the $t_{1/2},\lambda_z$ were 3.74 (±0.77) and 3.67 (±1.20) hr, respectively.

No statistically significant differences between the 1 and 2 mg doses were seen in the dose-normalized kinetic estimate for DD 01 C_{max} ($p = 0.389$) and $AUC_{0-\infty}$ ($p = 0.902$). No dose related changes were apparent in T_{max} ($p = 0.91$) or $t_{1/2},\lambda_z$ ($p = 0.187$) on Day 28. Metabolite kinetics at steady-state supported the assessment based on the parent drug of a lack of dose effect on kinetics.

In the poor metabolizers (n = 3), tolterodine C_{max} ranged from ng/mL, attained in ~1 hr. Consistent with the magnitude of the dextromethorphan phenotype estimate, the corresponding AUC_{0-12} (area over a dosing interval) ranged from ng.hr/mL and the CL_o from L/hr/kg. Due to bioanalytical limitations, tolterodine kinetics could not be estimated for one PM (#102).

Single versus Multiple Dose Pharmacokinetics

Multiple oral dosing (steady-state) with 1 mg resulted in no significant changes (signed rank test) in tolterodine T_{max} ($p = 0.25$), C_{max} ($p = 0.867$), AUC_{0-12} ($p = 0.432$), $t_{1/2},\lambda_z$ ($p = 0.695$), CL_o ($p = 0.509$) or V_d ($p = 0.769$) compared to the estimates following the first dose on Day 1. Similarly, no significant changes in pharmacokinetic parameters, attesting to a lack of accumulation, could be detected following the 2 mg twice daily regimen compared with the first dose kinetics. The steady-state/single dose ratios (R; accumulation factor) for C_{max} and AUC, estimating drug accumulation, were 1.05 and 1.25, respectively, following the 1 mg dose, while for the 2 mg dose these were 1.45 and 1.46. Although an increase of 46% in the mean C_{max} for tolterodine was observed when Day 28 data for the 2 mg are compared to the

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single dose; given the variability in EMs (due to phenotype status), this change was not statistically different (p = 0.211). The power was < 94% based on C_{max} estimate. Obviously, two subjects with relatively high C_{max} could account for increase in the mean C_{max} (see 95% CI). However, the steady-state (Day 28) mean AUC_{0-12} for tolterodine following the 2 mg dose was significantly (p = 0.027) higher compared to the $AUC_{0-\tau}$ estimate following the first dose (Day 1).

No significant changes were apparent in DD 01 kinetics following 1 and 2 mg doses of tolterodine that suggested drug accumulation. Interestingly, the DD 01 $t_{1/2},\lambda_z$ estimate increased significantly (p = 0.019) at steady-state (Day 28) following the 2 mg dose.

The ratio estimates for DD 01 C_{max} and AUC were 1.27, 1.15 (1 mg) and 1.12, 1.16 (2 mg), respectively, and did not suggest any accumulation. Overall, both the parent drug and the metabolite data failed to exhibit and support accumulation following 1 or 2 mg tolterodine b.i.d. regimen.

Dose-proportionality Assessment

The following analysis was performed in order to provide indications regarding dose proportionality or deviations from that and may serve as supportive data to a formal dose proportionality study. Figure 3 shows AUC vs. tolterodine dose regression (forced through zero) plots. Although limited in nature to address the dose-proportionality, these data are suggestive of proportionality based on single doses (r^2 = 0.183, slope = 4.95 [95% CI: 3.31-6.59]) and linear kinetics based on steady-state (r^2 = 0.198, slope = 7.10 [95% CI: 4.92-9.28]). The low coefficients of determination are reflective of the intersubject variability inherent in the magnitude of the extensive metabolizer phenotype. Given the degrees of freedom, the correlation coefficients for both regressions are statistically significant. The overlap (estimation error) in the slope estimates for the single and multiple dosing states appears to be related to this variation.

Sponsor's Conclusions:

- Relative to the placebo, both 1 and 2 mg tolterodine doses administered on a b.i.d. regimen for 28 days were well tolerated in elderly subjects (age: ≥70 years).

- Tolterodine and DD 01 kinetics in this cohort appear to be similar to those previously reported.

- Tolterodine kinetics following the 2 mg b.i.d. regimen suggested minor accumulation.

- There were no clinically significant findings with respect to safety variables, including ECG, blood pressure, heart rate, clinical chemistry or hematology.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0240

Study Number: 95-OATA-022

Title of the study The influence of food on the bioavailability of tolterodine. An open, single dose cross over study in healthy volunteers.

Objective: To study the influence of food on the bioavailability of tolterodine after a single dose administration of 2 mg.

Study Design: Open, single-dose, cross-over

Subjects: Twenty-four healthy females and males.

Study product: Tolterodine L-tartrate tablet, 2 mg Batch No. A 049404.

Statistical methods: Descriptive statistics, including means and standard deviations were calculated for the pharmacokinetic parameters. AUC_{∞} and C_{max} were evaluated with analysis of variance (ANOVA) and 90% confidence interval

Results

Table 47. Pharmacokinetic parameters (mean ± SD; median with range for t_{max}) for tolterodine and DD 01 after oral administration of tolterodine with and without food.

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_o (l/h)	209 ± 148	376 ± 382		

Table 48. AUC_{∞} and C_{max} ratios, i.e. relative bioavailability (geometric mean with 90 % CI) for tolterodine and DD 01. Treatment with food compared to fasting.

	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)

Sponsor's Conclusions:

- Bioequivalence could not be concluded for tolterodine when given with and without food. A 53% increase in serum levels (AUC_{∞}) was seen when the drug was given with food. However, more importantly, bioequivalence was shown for the active metabolite DD 01 with respect to both AUC_{∞} and C_{max}, when treatment with food was compared to fasting administration.

- Approximately 75 % of the systemically available tolterodine is metabolized to DD 01 by CYP2D6 in extensive metabolizers. This implies that other routes of elimination have a minor contribution to the systemic clearance. In the present study all subjects were extensive metabolizers. The effect of food on the pharmacokinetics of tolterodine in poor metabolizers can thus not be evaluated. However, assuming that the effect seen in extensive metabolizers is due to limited capacity of CYP2D6 (which is not present in poor metabolizers) no food effect is expected in the poor metabolizers.

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- *In vitro* data show that the free fraction of DD 01 is much higher than that of tolterodine which results in significantly higher concentrations of unbound DD 01 compared to tolterodine in extensive metabolizers. As a consequence of the equipotency of DD 01 and tolterodine it is likely that DD 01 accounts for most of the clinical effect in extensive metabolizers. The increased bioavailability of tolterodine is therefore not expected to be of any clinical relevance.

Reviewer's Comments:
The effect of food on the bioavailability of tolterodine in poor metabolizers (individuals genetically deficient in CYP 2D6) has not been assessed. In poor metabolizers, the primary pathway of elimination is metabolism by cytochrome P-450 3A4. A food effect may also occur in poor metabolizers and the assumption that no food effect is expected in the poor metabolizers due to lack of CYP 2D6 may not be valid.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0242

Study Number: CTN 95-OATA-024

Title of the study: Dose proportionality of tolterodine. An open, randomized, single-dose, cross-over study in healthy volunteers.

Objectives: The primary objective of this study was to compare the pharmacokinetics of tolterodine and DD 01, respectively, after single oral doses of 1, 2 and 4 mg.

A secondary objective of the study was to collect serum, after the 4 mg dose, for the possible identification/quantification of metabolites of tolterodine hitherto not studied in human serum.

Study Design: Open, randomized, 3-period cross-over, single-dose study.

Subjects : Twenty-four (11 males, 13 females)

Test product: Tolterodine tablets 1 mg, batch no. VC 800.

Duration of treatment: 3 single doses with a one week wash-out between doses.

Statistical methods: Dose proportionality was tested by using bioequivalence criteria on dose normalized, log-transformed AUC_∞ and C_{max} values for both tolterodine and DD 01 after administration of a single dose of tolterodine of 1, 2 and 4 mg.

Results: The pharmacokinetic variables are summarized in the following table:

Table 49

		1 mg		2 mg		4 mg	
Parameter[1]		Tolterodine	DD 01	Tolterodine	DD 01	Tolterodine	DD 01
AUC_∞	EM[2]	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[2]	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	

1: mean ± SD except t_{max} which is given as median (range)
2: EM = extensive metabolizers PM = poor metabolizers

The relative bioavailability (%) of the dose normalized 1 and 4 mg doses, compared to the 2 mg dose (geometric mean with 90% CI) are summarized in the following table:

Table 50.

	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)

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Sponsor's Conclusions:

- The pharmacokinetics of tolterodine, and its active metabolite DD 01, were found to be linear over the dosage range of 1 to 4 mg.

- The results indicate that the both the 1 mg and 4 mg doses are bioequivalent to the 2 mg dose after dose normalization. This means that there is a linear increase in AUC_∞ and C_{max} that is proportional to the increase in tolterodine dose. Although no formal statistical testing can be performed for the three poor metabolizers in this study, a comparison of their data for the different dose levels indicates that the pharmacokinetics of tolterodine and DD 01 are proportional to dose not only in extensive but also in poor metabolizers of debrisoquine.

- Marked increases (50-100%) in orosomucoid serum concentrations, and thus the protein binding of tolterodine were found to greatly increase tolterodine serum concentrations within individuals. This increase was also seen as a decrease in tolterodine clearance. Serum levels of DD 01 were also increased but to a lesser degree. As could be expected, the half-lives of tolterodine and DD 01 were not affected by the change in protein binding.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0244

Study Number: CTN 95-OATA-026

Title of the study: A Phase I, open label, safety and pharmacokinetic study of tolterodine in patients with hepatic cirrhosis.

Objectives: The objectives were to investigate the safety and pharmacokinetics of tolterodine and DD 01 in cirrhotic patients and to determine *ex-vivo* protein binding of tolterodine and DD 01.

Study Design: Open label, one period, single dose.

Subjects: Sixteen (16) patients with hepatic cirrhosis 1) according to Child - Pugh classification (Class A or Class B liver disease) or 2) proven by liver biopsy (preferred), or liver-spleen scan (^{99m}Tc-sulfur colloid) compatible with cirrhosis, including moderate, diffuse, non-homogeneous uptake of the radionuclide, and spleen uptake greater than the liver on the posterior view, and a compatible medical history of cirrhosis.

Study product: Tolterodine L-tartrate tablet, 2 mg Batch No. A 049404.

Duration & dosage: Twenty four (24) hours; A single 2 mg dose

Assay Methodology:

Results
The pharmacokinetics of tolterodine in cirrhotic patients are included in Tables 51 to 55.

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Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0245

Table 51. Pharmacokinetic Parameters of Tolterodine in Cirrhotic Patients by Genotype

Genotype		Weight (kg)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	Cl_o (L/hr/kg)	$t_{½z}$ (hr)
EM	Mean	87.3	5.7	1.0	44.1	57.7	1.0	7.8
	SD	14.8	3.4	0.4	34.2	59.4	1.7	4.7
	N	14	14	14	14	14	14	14
	Range							
PM	Mean	69.9	8.3	1.8	109	161	0.13	14.6
	N	2	2	2	2	2	2	2
	Range							

Table 52. Pharmacokinetic Parameters of DD 01 Post-Tolterodine in Cirrhotic Patients by Genotype

Genotype		Weight (kg)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{½z}$ (hr)
EM	Mean	87.3	1.4	1.7	12.2	14.8	9.8
	SD	14.6	0.85	0.9	6.72	7.32	7.2
	N	14	14	13	14	14	13
	Range						

A between study comparison of 2 mg single dose kinetic estimates from previous studies in normal elderly and healthy volunteers (EMs), statistically significant differences ($p < 0.05$) were apparent in tolterodine C_{max}, $AUC_{0-\infty}$, $t_{½z}$, and CL_o in cirrhotic patients. However, the tolterodine levels and half-life where lower than what is seen in healthy PMs. Such a change in kinetics was not unexpected, as hepatic metabolism to DD 01 is the primary route for tolterodine elimination in humans. Both AUC and half-life of DD 01 showed significant increases compared to estimates in EM healthy volunteers. However, DD 01 AUC was not higher in cirrhotic patients than in the elderly. Taking unbound serum concentrations into account , the total exposure in cirrhotic EMs is higher than in healthy EMs, both young and elderly. Also in cirrhotic PMs the exposure is higher than in young and elderly non-cirrhotic PMs. The exposure in cirrhotic patients appears to be about 25-50% higher than what is seen in non-cirrhotic individuals.

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Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0246

Table 53. Mean (± SD) Kinetic Parameters of Tolterodine in EMs Following a Single 2 mg Dose: Normal Healthy Volunteers(NHV), EM Elderly and EM Cirrhotic Patients

ESTIMATE	NHV (n = 21)	Elderly (n = 9)	Cirrhotic (n = 14)
Age: range (yr.)	21-42	> 75	42-68
C_{max} (ng/mL)	2.11 (2.6)	2.8 (2.1)	5.7 (3.4)
$AUC_{0-\infty}$ (ng·hr/mL)	7.49 (8.60)	8.76 (6.09)	57.7 (59.4)
CL_o (L/hr/kg)	5.65 (3.84)	3.02 (1.64)	1.0 (1.7)
$t_{½z}$ (hr)	2.63 (0.89)	2.16 (0.44)	7.8 (4.7)

Table 54. Mean (± SD) Kinetic Parameters of DD 01 in EMs Following a Single 2 mg Tolterodine Dose: Normal Healthy Volunteers(NHV), Elderly and Cirrhotic Patients

	NHV (n = 21)	Elderly (n = 9)	Cirrhotic (n = 14)
Age: range (y)	21-42	> 75	42-68
C_{max} (ng/mL)	2.2 (0.75)	3.5 (1.6)	1.4 (0.85)
$AUC_{0-\infty}$ (ng·hr/mL)	10.7 (3.85)	16.0 (8.05)	14.8 (7.32)
$t_{½z}$ (hr)	3.20 (0.76)	2.89 (0.37)	9.8 (7.2)

Table 55. Mean (± SD) Kinetic Parameters of Tolterodine in PMs Following a Single 2 mg Tolterodine Dose: Normal Healthy Volunteers (NHV), Elderly and Cirrhotic Patients

	NHV (n = 8)	Elderly (n = 11)	Cirrhotic (n = 2)
Age: range (yr.)	19-47	60-79	42-68
C_{max} (ng/mL)	10.0 (4.9)	n.a.	range: 6.4 - 10.2
$AUC_{0-\infty}$ (ng·hr/mL)	100 (51)	174 (112 - 271)[1]	range: 124 - 199
CL_o (L/hr/kg)		n.a.	0.09-0.16
$t_{½z}$ (hr)	6.5 (1.6)	n.a.	range: 13.5 - 15.7

1: Geometric mean with 95% confidence interval
n.a.: Not available

Protein Binding: Due to the small sample volumes available and high protein binding, tolterodine levels were measurable in only three of the 16 patients while DD 01 levels were detected in 10 patients. No apparent time dependence was evident in DD 01 binding from serum samples collected 2 or 8 hours post-dose. Thus, individual estimates for those were averaged.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0247

Mean percent tolterodine unbound (n=3) was 3.6±1.1% for an average orosomucoid concentration of 0.44 mg/mL. Percent DD 01 unbound (n=10) was 36±10% (18).

Blood pressure and heart rate: The magnitude of the change in these measures, from baseline (screening), at 2 hr post-dose and at follow-up are also provided. There were no notable or statistically significant changes in the means of any of the blood pressure or heart rate measurements, except for an increase in heart rate at follow-up compared to baseline ($p = 0.02$); this difference was only 10%.

ECG parameters: The magnitude of the change in these measures, from pre-dose (t=0), at 2 hr post-dose and at follow-up are also provided. There were no significant changes in any of these five parameters at 2 hr post-dose (time when tolterodine concentrations are highest). At follow-up, no significant differences were apparent for QT, QRS, and T-wave amplitude means. Though, QT_{max} and QT (Lead II) were significantly lower ($p< 0.033$) at follow-up compared to pre-dose, these changes were < 4%.

Adverse Events: These were recorded for 2 patients. However, only one of the reports (patient no 15; rash) is related to the treatment. The other two reports (patient no. 16) were recorded one and four days before dose, respectively. The events were mild in severity, and the patients completely recovered without any intervention. No serious AE occurred during this study.

Sponsor's Conclusions:
The disposition of orally administered tolterodine was altered in patients with impaired liver function assessed based on Child-Pugh criteria. In extensive metabolizers, hepatic insufficiency results in increased systemic exposure to the parent drug due to diminished drug clearance, while the difference in DD 01 concentrations is negligible Cirrhotic PMs also have higher tolterodine levels compared to healthy volunteers. Taking unbound concentrations of tolterodine and DD 01 into account, the total exposure in both EM and PM cirrhotic patients was approximately 25-50% higher than what is seen in non-cirrhotic individuals.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0248

Study Number: CTN 95-OATA-028

Title of the study: Relative bioavailability of tolterodine tablets from different production sites. An open, randomized, single-dose cross-over study in healthy volunteers.

Objectives: The objective of this study was to compare the bioavailability of tolterodine tablets 2 mg produced in Ascoli (Italy) compared to tolterodine tablets 2 mg produced in Malmö (Sweden), in order to show bioequivalence between the two production sites with respect to AUC and C_{max}.

Study Design: Open, randomized, 2-period cross-over, single-dose study.

Subjects: Twenty-four (9 male, 15 female) healthy female and male volunteers between 20 and 50 years of age were enrolled in the study.

Test product: Tolterodine tablets 2 mg produced in Ascoli, batch no. 6401.

Reference product: Tolterodine tablets 2 mg produced in Malmö, batch no. A049404.

Duration of treatment: 2 single doses with a one week wash-out between doses.

Statistical methods: Statistical methods: Bioequivalence was evaluated using back- transformed confidence intervals resulting from an ANOVA on log- transformed AUC and C_{max} values for tolterodine and DD 01, respectively.

Results
The pharmacokinetic variables are summarized in the following table:

Table 56

	Tolterodine		DD 01	
Parameter[1]	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		

1: mean ± SD except t_{max} which is given as median (range)

The relative bioavailability (%; mean and 90% CI) of the Ascoli tablet compared to the Malmö tablet was:

Table 57.

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

Sponsor's Conclusions:
Tolterodine tablets 2 mg produced in Ascoli, Italy are bioequivalent with respect to rate and extent of absorption to tolterodine tablets 2 mg produced in Malmö, Sweden.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0249

Study Number: CTN 95-OATA-020

Title of the study: Effect of tolterodine on cytochrome P450 isoenzymes determined by three probe drugs.

Objectives: To investigate the *in vivo* effect of tolterodine on debrisoquine hydroxylation (CYP2D6), omeprazole hydroxylation (CYP2C19), omeprazole sulphoxidation (CYP3A4) and caffeine metabolism CYP1A2).

Study Design: Open label with a non-randomised cross-over group design.

Number of subjects: 12 healthy volunteers.

Test product: Tolterodine L-tartrate tablet, 2 mg (Pharmacia & Upjohn) Batch No A 049 404

Probe drugs: Declinax® (debrisoquine) tablet, 20 mg Batch No B 1680. Losec® (omeprazole) enteric capsules, 20 mg Batch No UK 5427. Koffein® (caffeine) tablet, 100 mg (ACO) Batch No P3A 001.

Treatment: 4 mg b.i.d. for 6 days.

Results

The mean metabolic ratios are presented in Table 58. No statistically significant difference in the metabolic ratios of the three probe drugs was obtained during co-administration of tolterodine in EMs (CYP2D6). Neither in PMs (CYP2D6) a statistically significant difference in the metabolic ratios of the three probe drugs was obtained during co-administration of tolterodine, despite the 5-10 higher tolterodine concentrations

Table 58 Mean metabolic ratios for the three probe drugs in 8 EMs and 4 PMs (CYP2D6).

	EM / PM			
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

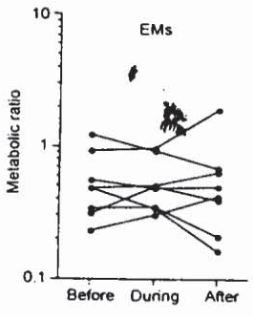

Figure 1 Metabolic ratio of debrisoquine (CYP2D6) before, during and after administration of tolterodine to EMs (CYP2D6).

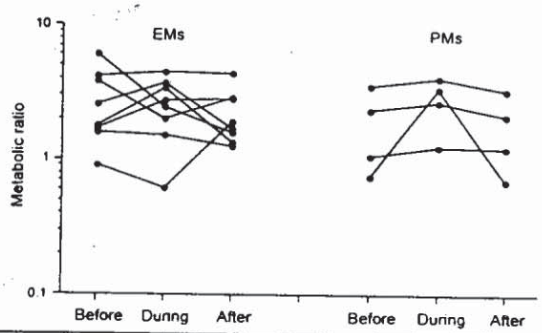

Figure 2 Metabolic ratio of omeprazole/hydroxy-omeprazole (CYP2C19) before, during and after administration of tolterodine to EMs and PMs (CYP2D6).

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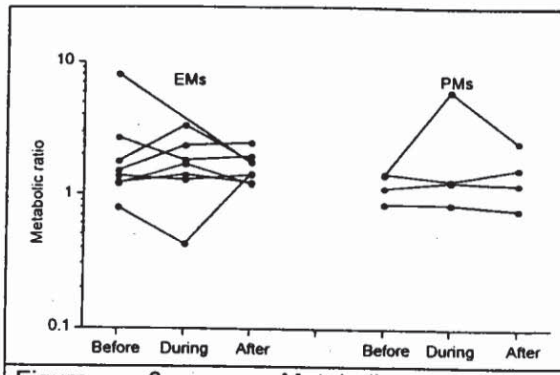

Figure 3 Metabolic ratio of omeprazole/omeprazole sulphone (CYP3A4) before, during and after administration of tolterodine to Ems and PMs (CYP2D6)

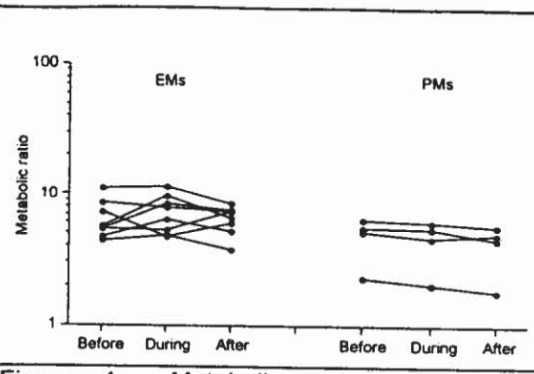

Figure 4 Metabolic ratio of caffeine/N3-demethylation (CYP1A2) before, during and after administration of tolterodine to EMs and PMs (CYP2D6).

Sponsor's 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 EMs nor PMs of CYP2D6 despite five to ten-fold higher concentration of tolterodine in PMs. 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.

Reviewer's Comment

The affect of these probe drugs on the pharmacokinetics of tolterodine has not been assessed herein.

APPEARS THIS WAY
ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0251

Study Number: CTN 95-OATA-030

Title of the study: The influence of fluoxetine on the safety and pharmacokinetics of tolterodine.

Objectives: The objectives of this study were to study the pharmacokinetics of tolterodine after 2 mg b.i.d. administration in psychiatric patients after co-administration of fluoxetine, 20 mg once daily and to study the safety and quantify dealkylated and carboxylated metabolites of tolterodine in serum and urine.

Study Design: This was an open, single sequence-group, cross-over study in psychiatric patients.

Subjects: 13 patients with depression or anxiety syndrome and subjective symptoms of urinary incontinence.

Test product: Tolterodine L-tartrate tablets 2 mg (Pharmacia & Upjohn AB) Batch no. VC 801.

Reference product: Fontex® capsules 20 mg (fluoxetine hydrochloride, Sweden AB) Batch no. B 2737CE.

Duration of treatment: Tolterodine L-tartrate, 2 mg b.i.d., Days 1-3 and Days 24-27. Fontex®, 20 mg once daily, were given on Days 4-27.

Results

A summary of the pharmacokinetic parameters of tolterodine and the different metabolites is given in Table 59.

Table 59. 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.

Substance and metabolic code		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	Ia	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 (hydroxylated tolterodine)	IIa	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
Dealkylated tolterodine[a]	Ib	n.a.	n.a.	n.a.	n.a.	3.9±2.2	1.2±0.47	11±5.5	21±14
Dealkylated hydroxylated tolterodine[b]	IIb	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Tolterodine acid	IVa	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	IVb	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

[a]Levels of dealkylated tolterodine <LOQ before interaction with fluoxetine. [b]Levels of dealkylated hydroxylated tolterodine <LOQ; n.a.: not applicable

A total of 16 adverse events were reported by 7 of the 13 patients during the study. The most frequent adverse event was headache, a side effect commonly reported during fluoxetine treatment.

Sponsor's Conclusions

- Fluoxetine significantly impaired the metabolism of tolterodine and an 4.8 fold increase of the AUC was seen in EMs.
- Only a minor change in AUC of DD 01 was seen during co-administration with fluoxetine in EMs.
- The AUC of tolterodine increased by 24% in the two PMs during fluoxetine administration.

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- No indications of influence of tolterodine and fluoxetine on the clinical and laboratory safety variables were seen.

Reviewer Comments:

1. Fluoxetine is primarily metabolized by CYP 2D6. Therefore, in extensive metabolizers, competitive inhibition of the metabolism of tolterodine to DD01 is likely and indeed, this was observed.

2. 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 CYP 2D6 also catalyzes the metabolism of DD01 to tolterodine acid and hence would also be inhibited by fluoxetine, this observation is not unexpected.

3. Although relatively weak, fluoxetine has been shown to have CYP 3A4 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 CYP 3A4.

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ON ORIGINAL

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0253

Study Number: CTN 95-OATA-025

Title of the study: A phase I, randomized, double-blind, placebo-controlled, kinetic-dynamic and safety drug interaction study of tolterodine and warfarin in healthy volunteers.

Objectives: The objectives were;
1. to assess warfarin effects on the coagulation time when coadministered with tolterodine. This assessment was focused on the mean PT-time profiles constructed using the AUC parameter estimates for tolterodine and placebo treatments.

2. to determine warfarin kinetics for both S- and R-isomers when coadministered with tolterodine. This assessment was focused on the AUC and the C_{max} of S- and R-isomers. Tolterodine/DD 01, C_{max} and AUC were also estimated in the presence and absence of warfarin.

3. to assess the safety of combined therapy of tolterodine with warfarin. The safety assessments included electrocardiogram, heart rate, blood pressure, hematology, and clinical chemistry tests on blood and urine.

Study Design: Randomized, double-blind, placebo-controlled, two-period cross-over (employing a priming dose of warfarin 3 weeks prior to the study initiation).

Subjects: Twenty (20) healthy volunteers

Test product: Tolterodine L-tartrate tablet, 2 mg (Pharmacia & Upjohn) Batch No VC 801

Duration & Dosage: Tolterodine 2 mg b.i.d. for 7 days; warfarin 25 mg once on Day 4

Assay Methodology:

Results
Concomitant tolterodine produced no discernible effect on the PT response or the factor VII profile observed following a single dose of warfarin. The difference in the mean AUC_{0-96} values of both treatment periods was < 4.5% for PT and < 7.5% for factor VII. The maximal responses (E_{max}) for the PT and factor VII were 10.82 sec, 80.1% in the placebo period and 10.96 sec, 75.1% in the tolterodine period, respectively.

Similarly, no statistically significant differences were apparent in R-and S-warfarin kinetic estimates of C_{max}, T_{max}, AUC_{0-96}, AUC_{∞}, or CL_o in the absence or presence of concomitant tolterodine. The elimination half-lives ($t_{½z}$) of R- and S-warfarin were slightly higher in the tolterodine period compared to placebo: 8% for R-warfarin and 4.9% for S-warfarin. This increase has no apparent clinical significance, as is evident from a lack of impact on coagulation time as assessed by PT and factor VII response to warfarin.

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No serious AEs were reported in this study. AEs were recorded for 8 subjects and the most frequent AEs were: five for headache (25%), three for coughing (15%) and two for abdominal pain (10%). These were mild to moderate in severity. No clinically significant changes were noted for vital signs (blood pressure, heart rate) or ECG parameters, within or between treatments. No clinically significant changes were apparent in select hepatic, renal, chemistry, hematology safety variables related to tolterodine, except for WBC and platelet ($p < 0.01$) at 48 hours post-warfarin dosing during treatment with tolterodine. At follow-up, however, no differences between either period were apparent. Several safety variables: bilirubin, globulin, BUN, hemoglobin, hematocrit, RBC and basophils showed significant changes ($p < 0.05$, Wilcoxon's signed rank) with both treatment arms at 48 hr post-dosing or at follow-up, relative to baseline, and could be most likely attributed to warfarin. Very small, but statistically significant differences between treatments were also seen in eosinophils ($p < 0.02$, t-test).

Table 60. Summary of Pharmacokinetics for R-Warfarin in the Absence or Presence of Tolterodine

		C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	CL_o (mL/Hr/Kg)	$t_{½z}$ (hr)
PLAC	Mean	1.52	1.65	57.06	69.10	4.59	37.27
	Median	1.51	1	56.65	68.31	4.39	37.26
	SD	0.23	1.09	10.67	14.44	1.23	6.93
	N	20	20	20	20	20	20
	Min						
	Max						
TOLT	Mean	1.48	1.95	57.98	72.49	4.37	40.28
	Median	1.47	2	59.63	70.67	4.34	40.39
	SD	0.21	1.15	9.82	17.41	0.98	8.53
	N	20	20	20	20	20	20
	Min						
	Max						

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Table 61. Summary of Pharmacokinetics for S-Warfarin in the Absence or Presence of Tolterodine

		C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	CL_o (mL/Hr/Kg)	$t_{½z}$ (hr)
PLAC	Mean	1.60	1.70	43.59	49.19	6.86	28.34
	Median	1.58	1	41.44	44.10	6.80	25.71
	SD	0.26	1.08	12.77	18.37	2.19	8.19
	N	20	20	20	20	20	20
	Min						
	Max						
TOLT	Mean	1.50	1.75	43.39	49.70	6.71	29.72
	Median	1.49	1	40.15	44.35	7.20	27.96
	SD	0.23	1.07	11.84	17.61	1.97	8.59
	N	20	20	20	20	20	20
	Min						
	Max						

Table 62. Summary of Pharmacokinetics for Tolterodine in the Absence or Presence of Warfarin

		C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-4} (ng.hr/mL)
Day 3	Mean	2.9	1.4	7.72
	Median	2.2	1.0	4.94
	SD	2.4	0.6	6.96
	N	20	20	20
	Min			
	Max			
Day 4	Mean	2.3	1.3	6.90
	Median	1.3	1.0	3.45
	SD	2.1	0.6	6.82
	N	19	19	19
	Min			
	Max			

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Table 63. Summary of Pharmacokinetics for DD01 in the Absence or Presence of Warfarin

		C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-4} (ng.hr/mL)
Day 3	Mean	2.4	1.5	6.72
	Median	2.4	1.0	6.33
	SD	1.1	0.6	2.78
	N	20	20	20
	Min			
	Max			
Day 4	Mean	2.0	1.2	6.25
	Median	1.9	1.0	6.14
	SD	0.78	0.5	2.43
	N	20	20	20
	Min			
	Max			

Table 64. Summary of Pharmacodynamics of Warfarin in the Presence or Absence of tolterodine

Variable		Treatment			
		Warfarin + Placebo		Warfarin + Tolterodine	
		Mean (SD)	Range	Mean (SD)	Range
PT	AUC_{0-96} (sec.hr)	485.5 (295.8)	161.4-1067	507.3 (366.9)	123.8-1359
	E_{max} (sec)	10.82 (5.72)	4-22.5	10.96 (6.06)	2.6-24.3
	t_{max} (hr)	31.1 (8.57)	16-54	35.5 (9.92)	24-54
Factor VII	AUC_{0-96} (%.hr)	4434 (1241)	2682-6548	4105 (1357)	2226-6763
	E_{max} (%)	80.1 (13)	61-115	75.1 (12.8)	46-99
	t_{max} (hr)	27.8 (4.2)	16-36	29.2 (5.7)	24-48

Sponsor's Conclusions:

Concomitant administration of tolterodine and warfarin to healthy volunteers did not result in any clinically significant changes in warfarin dynamics (e.g., PT and factor VII responses) or in kinetics of R- and S-isomers. Further, a single warfarin dose did not affect steady-state kinetics of tolterodine or its hydroxylated metabolite DD 01. Therefore, combined tolterodine and warfarin dosing is deemed safe and well tolerated.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0257

Study Number: CTN 95-OATA-027

Title of the study: Influence of tolterodine on the pharmacokinetics of Neovletta®, an oral contraceptive. An open, randomized, multiple-dose cross-over study in healthy volunteers.

Objectives: The objectives of this study were to investigate if tolterodine, 2 mg b.i.d. for 14 days, affects the pharmacokinetics (AUC, C_{max}, C_{min}) of ethinyl estradiol and levonorgestrel in women using this oral combination contraceptive and to determination of serum levels of progesterone and estradiol at selected time points to assess the possible risk of ovulation.

Study Design: Open, randomized, 2-period cross-over, multiple-dose study.

Subjects : Twenty-four healthy female volunteers between 20 and 40 years of age were studied.

Test product: Tolterodine tablets 2 mg, batch no. VC 801. Neovletta tablets, batch no. 44006

Duration of treatment: Neovletta for 21 days in each of two periods; Tolterodine for 14 days during one of the Neovletta periods.

Results

The result of the pharmacokinetic analysis is presented in the following table (mean ± SD with the exception of t_{max} which is given as median(range).):

Table 65

Pharmacokinetic variable:		AUC_τ (ng·h/l)	C_{max} (ng/l)	C_{min} (ng/l)	t_{max} (h)
Ethinyl estradiol	Without tolterodine	864 ± 284	99.7± 29.0	14.0 ± 8.2	1 (0.5 - 3)
	With tolterodine	808 ± 270	90.0 ± 29.2	13.8 ± 6.6	1.5 (1 - 12)
Levonorgestrel	Without tolterodine	79.4 ± 30.5	6.77 ± 2.09	2.02 ± 0.84	1 (1 - 24)
	With tolterodine	70.4 ± 20.3	5.80 ± 1.25	1.79 ± 0.57	1.5 (1 - 12)

The relative bioavailability (%) of the OC during the tolterodine treatment period, compared to the tolterodine-free treatment period is presented in the following table (geometric mean with 90% CI):

Table 66.

	AUC_τ	C_{max}	C_{min}
Ethinyl estradiol	93.5 (85.4 - 102.3)	90.1 (82.5 - 98.4)	104.9 (79.6 - 138.2)
Levonorgestrel	90.3 (84.6 - 96.4)	86.9 (80.7 - 93.6)	90.5 (84.7 - 96.6)

Sponsor's Conclusion:

No pharmacokinetic or pharmacodynamic interaction was found between tolterodine and an oral contraceptive containing ethinyl estradiol and levonorgestrel.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0258

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-771

ADMINISTRATIVE DOCUMENTS

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0259

Division Director NDA REVIEW

MAR 16 1998

NDA: 20-771 Detrol (Tolterodine) tablets 1 and 2 mg strength

Sponsor: Pharmacia and Upjohn

Submission date: March 24, 1997

Date of Review: March 16, 1998

This application presents background, protocols, and results from several clinical and pharmacokinetics studies in support of tolterodine (1 and 2mg orally, bid), an antimuscarinic agent, for the requested indication of the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Chemistry and manufacturing controls information as well as an appropriate pharmacology package are also included.

A synopsis will be made here of the reviews of this application as well as a recommendation to the Office of Drug Evaluation II of approval for the indication of "treatment of bladder overactivity with symptoms of urinary frequency, urgency or urge incontinence".

Physiology and Background

As noted in the Medical Officer review: detrusor muscle contractions are mainly mediated through cholinergic, muscarinic receptor stimulation. Inappropriate detrusor contraction can lead to a sensation of urgency. Increased urgency can lead to urinary frequency, nocturia and "urge incontinence" (if the urge to void cannot be resisted). The main pharmacologic therapy for this condition is directed at reducing the activity of the detrusor muscle with antimuscarinic agents.

Oxybutynin, an anti-cholinergic, anti-muscarinic agent is currently the most commonly prescribed therapy for urge incontinence. As would be expected from an anti-cholinergic agent, side effects such as dry mouth, reduced visual accommodation and constipation are common (often leading to discontinuation of drug therapy). This sponsor asserts that tolterodine is a competitive muscarinic antagonist that exhibits selective antimuscarinic activity for bladder receptors as compared to receptors in the salivary gland. Because of this "selectivity" the sponsor anticipated effectiveness similar to oxybutynin with an improved side effect profile (especially as relates to symptoms of dry mouth).

Important in the consideration of the safety of this product is the consideration of terodiline, a close chemical structure cousin of tolterodine. Terolidine is a product that was once approved in Sweden for the indication of angina pectoris and later withdrawn from the market due to safety

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reasons. This drug was found to have calcium channel blocking as well as other effects which increased the QT interval in humans which appeared to be associated with ventricular dysrhythmias including torsades de pointes. The marketing of terodiline was therefore halted. Because of the similarity of the two drugs, tolterodine was extensively tested for this association and none was found (see pharmacology, biopharmaceutics and medical officer safety reviews).

As discussed in the primary reviews, tolterodine is metabolized (with active metabolites) by the cytochrome P450 system. The issue of possible accumulation in "poor metabolizers", especially those taking concomitant medications which might block the alternative metabolic pathway, is discussed fully in the Clinical Pharmacology and Biopharmaceutics review. The clinical reviewer concludes that the adverse event profile comparison between "poor" and "extensive" metabolizers was not significant and the team recommends labeling to alert providers and users of the potential metabolism/accumulation issues.

Chemistry

Chemistry review issues were conveyed to the sponsor during the review process. Each were adequately addressed. Of note is the tradename change from the original proposal of to the revised name, "Detrol". Needed labeling changes have been made. After discussion between this Division and the Division of Drug Marketing, Advertising and Communications, a , initially proposed as part of the trade name, has been removed from the tradename logo but will remain as part of promotional materials (separate from the name).

Pharmacology/Toxicology

As per the pharmacology review, tolterodine has been adequately tested in mice, rats and dogs. Little to no organ toxicity (other than that expected due to the antimuscarinic pharmacodynamic effects) was produced by tolterodine. The analyses of non-human pharmacokinetics results as well as specific cardiac monitoring in the preclinical studies support the conclusion that there exists an adequate safety margin to support human safety for both the "poor" and "extensive" metabolizer.

Biopharmaceutics

The Office of Clinical Pharmacology and Biopharmaceutics has provided an extensive review of the issues of protein binding, metabolism, pharmacokinetics, special populations and drug interactions. Much of the safety concerns raised relate to the metabolism/elimination of tolterodine via hepatic metabolism and specifically through the catalytic activity of cytochrome P450 2D6 and 3A4. Cytochrome P450 2D6 is a genetically polymorphic enzyme that is absent in approximately 7% of Caucasians, 1% East Asians and 1% Black Americans.

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In looking at the metabolism data it appears that in extensive metabolizers, tolterodine acid and dealkylated hydoxylated tolterodine are present. In poor metabolizers, only dealkylated tolterodine was found. These findings are consistent with the predicted metabolic pathways. The final conclusion on this issue by the biopharmaceutics reviewer is that, although a theoretical risk of increased exposure exists, there appears to be no accumulation of tolterodine or its dealkylated metabolite in extensive metabolizers and no accumulation of dealkylated tolterodine in poor metabolizers after multiple dosing of 2 mg bid.

From review of drug-drug interaction studies, and based on the known metabolic pathways, the reviewer cautions that care should be taken when co-administering cytochrome P450 3A4 inhibitors (such as ketoconazole) along with Detrol. The reviewer recommends a starting dose of 1 mg in subjects with hepatic insufficiency and subjects with such concomitant drug use.

In terms of safety concerns related to the close chemical structure to terodiline, ECG data were scrutinized in Phase II and III studies and showed no difference in QT interval changes in tolterodine versus placebo treated subjects. This data also revealed showed no ECG differences in poor versus extensive metabolizers of tolterodine.

After further discussion in an OCPB briefing on March 11, 1998, it was decided that the sponsor should perform (Phase 4) a multiple dose pharmacokinetics and pharmacodynamic study in patients with hepatic impairment to assess the potential for ECG changes. Such a study would be proposed to the IND and performed within one year of approval. This Phase 4 commitment was discussed and agreed with the sponsor on March 12, 1998.

Clinical/Statistical

Three placebo-controlled, 12-week studies (studies 008, 009 and 010), constitute the pivotal clinical trials contained in this submission and involved randomization of 886 subjects (478 to tolterodine) with "detrusor overactivity" or "detrusor instability". Two of the studies (008 and 010) also incorporated an active control--Oxybutynin. The Medical Officer review describes the inclusion/exclusion criteria as well as baseline characteristics of those entered.

Along with the "pivotal" efficacy studies presented, the sponsor presents a total safety data base of 1645 subjects who took tolterodine for 6 months and 812 with 12 months of drug exposure.

The primary endpoint stated for the central studies was the change in mean number of micturitions per 24 hours from baseline to end of study (12 weeks). Secondary endpoints included an analysis of changes in mean number of incontinence episodes per 24 hours and mean volume voided per micturition.

For the primary endpoint (number of micturitions), tolterodine proved superior to placebo in two of the three central studies (008 and 009). In terms of change in mean volume voided per micturition, tolterodine was superior to placebo in all three studies. In none of the studies was

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tolterodine found to be superior to placebo for changes in mean number of incontinence episodes per 24 hours (although in each study tolterodine appeared to be more efficacious in this parameter, the difference did not reach statistical significance).

The sponsor submitted an analysis of pooled data for the three studies. The medical reviewer believes that the pooling is appropriate as the protocols of the studies were virtually identical. When the data from both the individual and pooled analyses are considered, superiority of tolterodine 1 and 2 mg over placebo with regard to change in mean number of incontinent episodes per 24 hours is demonstrated. The pooled data support the individual study findings of superiority in regards to micturition numbers and voided volume parameters.

The statisticians have debated the merits of the pooling of the data from these three trials. Although the protocols are similar, there is a question of whether the sponsor employed a reclassification of patients (based on change of dose group during the study) which weakens their statistical argument for support. The medical officer continues to believe that urgency, frequency and eventual urge incontinence exist as a continuum of symptoms and that this product, with its confirmed mechanism of action, is appropriate for approval for the complete spectrum of symptomatology.

It should be noted that in the phase 3 clinical studies no statistically significant efficacy or safety differences between tolterodine 1 and 2 mg were demonstrated. Some trends in the data indicate that tolterodine 2 mg is more active than tolterodine 1 mg.

In those studies where oxybutynin (5 mg tid) was used an active comparator, oxybutynin tended to demonstrate increased efficacy compared to tolterodine. In one of the central studies, oxybutynin was statistically significantly superior to tolterodine in increasing the volume voided per micturition--a measure of antimuscarinic effect on the bladder. As noted in the clinical review, it is likely that tolterodine, given in equi-potent doses (in terms of antimuscarinic effects) would have similar effects as oxybutynin. The trials presented in this application do not appear to compare equi-potent doses (in terms of both effectiveness and side effect profile) of the two products.

Safety information is extensively reviewed in the MO review dated March 10, 1998. Serious adverse events and deaths reported appeared to be related to underlying medical conditions, advanced age, etc.. None could be clearly attributed to tolterodine use.

The most commonly reported adverse event was dry mouth. The incidence of dry mouth tended to be higher in the tolterodine groups (24-50%) than in placebo groups (13-21%) and highest in the oxybutynin groups (69-86%). The incidence of other antimuscarinic side effects (constipation, abnormal accommodation, constipation and urinary retention) was low and did not clearly demonstrate an increase over background rates.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0263

Although the annoying side effect of "dry mouth" appears to be less with tolterodine than with the active comparator, it is noted that the incidence remains significant and that these trials were not designed to confirm superiority of tolterodine over oxybutynin for this endpoint. If a claim for decreased side effects such as dry mouth is to be made, at least one trial to assess this endpoint (in an adequately designed study) would be needed. Such a design would likely include a validated scoring/index system with set recording times, a clear definition of the endpoint, an agreed upon clinically meaningful difference between therapies for the endpoint and a rigorous attempt to assure equi-potent doses amongst the products compared in the study. These criteria were not met in any of the studies presented in this application.

In terms of monitoring for cardiac safety, the data from the pivotal as well as long-term safety studies gave no indication that tolterodine precipitated cardiac events. In the analyses, tolterodine use was not associated with lengthened QT intervals, other ECG changes, arrhythmias or other clinical signs and symptoms of cardiac disease.

RECOMMENDATION:

As per the review team conclusions, approval is recommended. Labeling discussions have been productive and the Division supports the labeling as proposed in the March 12, 1998 submission. The Phase 4 commitment for has been incorporated into the action package.

3/16/98 /S/

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Products, HFD-580

cc:
archival
HFD-580
HFD-580\LRarick, DShames, ADunson, LKammerman, BTaneja, ADorantes, GBarnette, AJordan, MRhee
HFD-102\JBilstad

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0264

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Group Leader's Memo

No Group Leader's memo will be prepared; comments will be provided in the Division Director Memo.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0265

NDA 20-771
DETRUSITOL™ Tablets

XIII. PATENT INFORMATION

PATENT CERTIFICATION

1.	Active Ingredient	Tolterodine L-Tartrate
2.	Strength(s)	1 mg and 2 mg
3.	Trade Name	DETRUSITOL™ Tablets
4.	a. Dosage Form	Tablets
	b. Route of Administration	Oral
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	20-771
7.	NDA Approval Date	To be determined
8.	Exclusivity - Date first ANDA could be approved and length of exclusivity period.	Five (5) years after date of NDA approval.
9.	Applicable patent numbers and expiration date of each.	5,382,600 Expiration date-2012 Claims cover 3,3-diphenylpropylamines, including tolterodine, and pharmaceutical compositions comprising them.

This is to certify that the above information is correct to the best of my knowledge.

Kerstin Franzén
Director of Regulatory Affairs
Pharmacia & Upjohn AB
Sweden.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0266

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A/BLA # 20-771 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-580 Trade and generic names/dosage form: DETROL Tablets (tolterodine tablets) Action: (AP) AE NA

Applicant Pharmacia & Upjohn Therapeutic Class 15 / MUSCARINIC RECEPTOR ANTAGONIST

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __ c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

_____ /S/ 3/5/98

Signature of Preparer and Title Date

cc: Orig (NDA) BLA # 20-771
HFD-580 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0267

DEBARMENT CERTIFICATION

Detrol™
tolterodine tartrate tablets
(NDA 20-771)

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Edward L. Patt

2/13/98

Ed L. Patt
Manager
Regulatory Compliance

Date

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0268

NDA 20-771
DETROL Tablets (tolterodine tablets)

Safety Update Review

Included in Medical Officer review dated March 5, 1998.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0269

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 6, 1998

FROM: Lisa A. Kammerman, Ph.D., Team Leader (HFD-715) LAK 3/6/98

THROUGH: S. Edward Nevius, Ph.D., Division Director (HFD-715) SEN 3/6/98

TO: NDA 20-771

SUBJECT: Team Leader Memorandum: NDA 20-771 (Tolterodine)

This memorandum provides additional statistical comments on NDA 20-771, and on Dr. Baldeo Taneja's statistical review of the submission.

Dr. Taneja's comments on sponsor's results (p. 18 of his review)
For ease of discussion, the following table summarizes the results (p-values) of the sponsor's analysis of the three placebo-controlled studies (008, 009, and 010) contained in the submission. Dr. Taneja's review gives a detailed discussion of the analyses.

Summary of p-values for comparisons with placebo

		Endpoint (change from baseline at 12 weeks)		
Study #	Treatment Arm	Micturitions	Incontinence Episodes	Volume Voided
008	Oxybutynin 5 mg	.0680	.023	.0001
	Tolterodine 2 mg	.0022	.22	.0001
009	Tolterodine 2 mg	.0045	.19	.0001
010	Oxybutynin 5 mg	.29	.0012	.0001
	Tolterodine 2 mg	.27	.13	.015

Note: Entries in table are taken from Dr. Taneja's review.

The applicant apparently performed repeated measures ANOVA to compare the time course among treatment groups for each of the endpoints within each of the studies (see page 2 of Dr.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0270

Taneja's review). The p-values in the above table result from linear contrasts at Week 12. Given that the regulatory decision is being made on change from baseline at Week 12, Dr. Taneja should have addressed the appropriateness of this approach. However, his nonparametric analyses using change from baseline at Week 12 appear to support the findings presented by the applicant.

Volume voided

These results indicate that tolterodine and oxybutynin are superior to placebo in volume voided at 12 weeks relative to baseline. The medical reviewer considers volume voided to be the most important endpoint for evaluating physiological changes.

Micturitions

For the micturitions endpoint, my conclusion is that tolterodine 2 mg is significantly better than placebo. This was demonstrated in two of the studies (008 and 009). Because oxybutynin did not beat placebo in Study 010, the lack of assay sensitivity for this endpoint may explain the nonsignificant comparison between tolterodine 2 mg and placebo.

As Dr. Taneja's review indicates, the protocols for these studies were powered for this endpoint. I agree with his general concern that oxybutynin, a product approved for the proposed indication, did not beat placebo in two of the studies. This is especially true for Study 010. Dr. Taneja's review should have explored potential reasons for Study 010's inability to detect a significant difference from placebo for either treatment arms. For example, an assessment could consider whether the conduct of Study 010 differed from the other studies, and whether study drug discontinuations made an impact.

Incontinence episodes

For the endpoint of incontinence episodes, tolterodine 2 mg did not beat placebo in any of the three studies. In contrast the oxybutynin treatment arm in the two studies containing an active control arm was significantly better than placebo. Thus the lack of statistical significance in these two studies cannot be explained by the absence of assay sensitivity for incontinence episodes. Study 009 did not contain an active control arm; thus, the issue of assay sensitivity cannot be addressed for this study.

Even considering that oxybutynin was superior to placebo in the two studies with an active control, one might argue the studies may have been underpowered to detect a tolterodine treatment effect. The results from Studies 008 and 010 suggest tolterodine apparently has a smaller treatment effect than oxybutynin; thus a larger study would be needed to detect a statistically significant difference between tolterodine 2 mg and placebo. A determination of the clinical relevance of such a difference would need to be made.

According to the medical officer and the statistical reviewer, these studies were similar in design. Therefore, under certain circumstances it may be possible to pool the data from these studies to estimate the treatment effect of tolterodine compared with placebo on the endpoint of incontinence episodes. The next section addresses this issue.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0271

Applicant's pooled analysis:
Other than stating that the pooled analysis needed to be stratified by study, Dr. Taneja's review does not adequately critique the applicant's pooled analysis (summarized starting on page 14 of his review) nor indicate why the applicant submitted it. According to his review, the pooled analysis appears to have reclassified the patients randomized to tolterodine 2 mg: those who remained on tolterodine 2 mg throughout the study were called "tolterodine 2 mg"; those whose dose was reduced to tolterodine 1 mg were called "tolterodine 1 mg". On its face, the reclassification of patients is inappropriate; the data should be analyzed according to the way patients were randomized.

Typically in assessing endpoints from adequate and well-controlled studies, the results from each study needs to stand on its own. Under certain circumstances, appropriate analyses of pooled data can be used to provide an estimate of the treatment effect. For this NDA, the medical reviewer and statistical reviewer have indicated that the study designs were similar in design. Thus, a confidence interval on the difference between tolterodine 2 mg and placebo, constructed by stratifying on study and classifying patients according to the treatment group to which they were randomized, may be appropriate for providing an overall estimate of the treatment effect for the various endpoints.

Other unresolved issues

Adjustments for multiple endpoints
The issue of whether the analyses should have adjusted for multiple endpoints was not addressed in Dr. Taneja's review.

Interpretation of subgroup analyses
A more appropriate assessment of whether the treatment effects were consistent among the various subgroups defined by age, race, and gender would have included calculation of the mean treatment effect (i.e., drug - placebo difference) for the various subgroups.

Discrepancies in data
Dr. Taneja performed nonparametric analyses on datasets provided by the applicant. There are inconsistencies between the number of patients with data in these datasets and with what was provided in the study reports. For example, Dr. Taneja's analysis of Study 009 indicates that for number of micturitions, 128 patients randomized to tolterodine 2 mg and for number of incontinence episodes, 116 patient randomized to tolterodine 2 mg were included in the analyses. This contrasts with the applicant's analysis: for micturitions, 129 patients randomized to tolterodine 2 mg and for incontinence episodes, 117 patients randomized to tolterodine 2 mg were included in the analyses. These discrepancies should be addressed by the applicant.

Summary
As noted above, the statistical review failed to address several key issues that should be included in an addendum review. However, I do concur with Dr. Taneja's basic conclusions:

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0272

Reduction in micturitions per 24 hours from baseline to 12 weeks:

Tolterodine 2 mg was significantly better than placebo in two studies (008 and 009) but not the third (010).

Increase in volume voided per micturition from baseline to 12 weeks:

Tolterodine 2 mg was significantly better than placebo in all three placebo-controlled studies (008, 009, 010)

Reduction in incontinence episodes per 24 hours from baseline to 12 weeks:

Tolterodine 2 mg was not significantly better than placebo in any of the three placebo-controlled studies.

cc:
Archival
HFD-580
HFD-580/DShames, ADunson
HFD-715/ENevius, LKammerman, BTaneja

LAK/WinWord7.0/Reviews/Tolterodine/Team Leader Memo 980305

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0273

HFD 530/ Boring

(823)

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: **Dan Boring, Chair, HFD-530, Corporate Building Room N461**

FROM: Division of Reproductive and Urologic Drug Products HFD-580
Attention: Bob Seevers /S/ 4/24/97 Phone 301-827-4240

DATE: April 24, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Detrusitol tablets NDA 20-771

Company Name: Pharmacia & Upjohn

Established Name, including dosage form: Tolterodine tablets

Other trademarks by the same firm for companion products: None

Indications for Use: Treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms

Initial comments from the submitter: (concerns, observations, etc.) . None

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Response will be as timely as possible.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0274

Consult #823 (HFD-580)

DETRUSITOL tolterodine tablets

The Committee noted one look-alike/sound-alike conflict: DETUSSIN. Since DETUSSIN is an OTC cough preparation, the Committee felt there was a low potential for confusion. There were no misleading aspects found with the proposed name.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 8/18/97, Chair
CDER Labeling and Nomenclature Committee

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0275

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Microbiology Review

No microbiology review is required.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0276

DEPARTMEN. OF HEALTH & HUMAN SERVICES

Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-771

JAN 16 1998

Pharmacia & Upjohn
Attention: Ilze K. Antons, M.S.
Senior Regulatory Manager
Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Antons:

Please refer to your pending March 24, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrusitol™ tablets (tolteridine tablets).

We also refer to your amendments dated August 29, 1997, November 18, 1997, November 18, 1997, and December 31, 1997.

We have completed our review of the chemistry section of your submission and have identified the following deficiencies:

The following items concern the drug substance:

Specifications

1. Although you have submitted an in-process limit test for in the drug substance, this test should be part of the drug substance release specifications. Please include a limit test for in the drug substance release specifications.

2. The analytical and stability data on the twelve batches of the drug substance submitted indicate that organic impurities are low (less than %). Most of these batches were used for toxicology and clinical studies which means that the proposed impurity specifications should be tightened: Total NMT %, CA 020045 NMT %, FC 97A NMT % and Sum of Unspecified Impurities NMT %. This change should also be made to the drug substance stability protocol.

The following items concern the drug product:

Regulatory Specifications

The organic impurities limits at expiry need to be tightened. Based on the stability data submitted, the limits should be: Total Organic Impurities NMT %, CA 020045 NMT %, and FC 97A NMT

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0277

%. The same change should be made in the post-approval stability protocol.

Container/Closure System

1. A deficiency letter has been sent to the in regard to their DMF for

2. You have not provided any information on the use of either a cap liner or innerseal for the bottles. If a cap liner or innerseal will be used, please submit appropriate descriptions of the nature and source of the materials.

Labeling

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely.

/S/ 1/16/98

Lisa D. Rarick, M.D.
Director,
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0278

cc:
Original NDA 20-771
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/RSeevers/MRhee
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: JMarkow/January 15, 1998/20771.01n
Initialed by:
final:

INFORMATION REQUEST (IR)

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0279

Dunson

MEMORANDUM OF TELECON

DATE: November 12, 1997

APPLICATION NUMBER: 20-771; Detrusitol

BETWEEN:

Name: Susan Mandabough
Phone: (616) 833-4070
Representing: Pharmacia & Upjohn

AND

Name: Robert Seevers, Ph.D., Moo-Jhong Rhee, Ph.D, and Mr. Alvis Dunson
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To discuss the addition of in-process controls for the super-potency tablets.

SUMMARY:

The sponsor was informed that in-process controls should be included in batch runs and especially at the end of the runs to ensure super-potency tablets are not being manufactured. The test need only be performed on the next two batches of each strength (1.0 mg and 2.0 mg) tablets with a concentration on testing at the end of the run where the problem occurred. Further testing would no longer be needed once satisfactory results on two additional runs for each strength have been achieved demonstrating that super-potency does not occur.

This proposal should be submitted as a minor amendment to the NDA with no affect on the review clock.

/S/ 12/8/97

Alvis Dunson
Project Manager

/S/ 12/8/97

Robert Seevers, Ph.D.
Chemist

cc: Original 20-771
HFD-580/Div. File
HFD-580/Alvis Dunson
HFD-580/RSeevers/MRhee

Drafted by: ADunson/November 20, 1997/n20771tc

Concurrence:
RSeevers11.22.97/MRhee12.2.97

TELECON

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0280

Dunson

NDA 20-771

APR 9 1997

Pharmacia & Upjohn
Attention: Ilze K. Antons, M.S.
Senior Regulatory Manager
Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Antons:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Detrusitol™ Tablets (tolterodine tablets)
Therapeutic Classification:	Standard
Date of Application:	March 24, 1997
Date of Receipt:	March 25, 1997
Our Reference Number:	20-771

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 24, 1997 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102© of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review, but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0281

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

/S/ 4/7/97

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-771
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/DShames/HJolson/MRhee/AJordan/ADorantes/LKammerman/LPauls
DISTRICT OFFICE

Drafted by: ADunson/March 27, 1997/n20771ak

ACKNOWLEDGEMENT (AC)

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0282

MEMO OF TELECON

NDA: 20-771

Drug: DETROL (tolterodine tartrate tablets)

Date: March 18, 1998

Time: 2:00 PM

External Participant: Pharmacia & Upjohn

Tele: 616-833-8239

FDA Attendees:

Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Gregory Shawaryn - Regulatory Affairs

Conversation:

The following Clinical Pharmacology comments were conveyed:

1. Please submit 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. The full study report can be submitted for review post-approval.

2. The proposed *in vitro* dissolution test method is acceptable. However, it is recommended that the drug release specifications be changed to Q= \% at minutes. This issue should be addressed prior to approval.

/S/

Alvis Dunson 3/18/98

drafted: ADunson/3.18.98/n771tc6

cc:
IND Arch:
HFD-580
HFD-580/ADunson/DShames/LRarick/GBarnette

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0283

MAR 1 8 1998

MEMO OF TELECON

NDA: 20-771 **Drug:** DETROL (tolterodine tartrate tablets)

Date: March 12, 1998 **Time:** 11:00 AM

External Participant: Pharmacia & Upjohn **Tele:** 616-833-0856

FDA Attendees:

K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Susan M. Mondabaugh, Ph.D. - Director, U.S. Regulatory Affairs

Conversation:

The following comments were conveyed:

Since tolterodine is eliminated primarily through metabolism, a significant safety concern exists in patients with hepatic impairment. In pharmacology/toxicology studies in dogs it was observed that after nine days of treatment with tolterodine there was a percent increase in the Q-Tc interval . A single dose pharmacokinetic study was conducted in patients with hepatic cirrhosis and an increase in bioavailability and a decrease in clearance compared to that seen in normal healthy volunteers was observed.

Therefore, we request that you conduct a multiple-dose pharmacokinetic/pharmacodynamic study in hepatic impaired patients in which steady state pharmacokinetic and electrocardiogram (ECG) changes are assessed. Please submit a study design that includes the number of patients, duration of treatment, and time of ECG for review prior to initiating the study. This study may be conducted post-approval.

/S/ 3/16/98
Alvis Dunson

/S/ 3/18/98
Gary Barnette, Ph.D.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0284

MEMO OF TELECON

NDA: 20-771

Drug: DETROL (tolterodine tartrate tablets)

Date: March 4, 1998

Time: 11:00 AM

External Participant: Pharmacia & Upjohn

Tele: 616-833-0856

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Daniel Shames, M.D. - Medical Officer, DRUDP (HFD-580)
K. Gary Barnette, Ph.D. - Pharmacokinetics Reviewer, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Alex Jordan, Ph.D. - Pharmacologist, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituent:

Kenneth King, Ph.D. - Vice President, Worldwide Regulatory Affairs
Susan M. Mondabaugh, Ph.D. - Regulatory Affairs

Conversation:

The sponsor wanted to clarify issues related to the physician labeling insert for DETROL. The following comments were conveyed:

1. The sponsor wanted to revise the introductory text in the **CLINICAL PHARMACOLOGY** section of the labeling to retain the reference to the anethesized cat data that indicated tolterodine shows a selectivity for the urinary bladder over salivary glands. The sponsor agreed to modify the statement and submit for review.

2. The sponsor indicated that the anethesized cat data was viewed as basic pre-clinical data to understand the drug and no advertising claim is expected.

/S/ 3/4/98
Alvis Dunson

/S/ 3/12/98
Lisa Rarick, M.D.

Post Meeting Note:

The sponsor faxed an unofficial version of the proposed carton and container labels for Division comment on February 24, 1998, followed by an official submission on February 25, 1998.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0285

drafted: ADunson/3.5.98/n771tc4

Concurrences:
GBarnette/AJordan/DShames3.9.98/LRarick3.10.98

cc:
IND Arch:
HFD-580
HFD-580/ADunson/DShames/LRarick/GBarnette/AJordan

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0286

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0287

NDA 20-771
DETROL Tablets (Tolterodine Tablets)

Federal Register Notices

This application was not the subject of any Federal Register Notices.

Patent Owner, UCB Pharma GmbH – Exhibit 2072 - 0288