

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:

Reviewer Name: Laurie McLeod

Division Name: Division of Reproductive and Urologic Drug Products

HFD-580

Review Completion Date: 2 June 2000

IND/NDA number: NDA 21-228

Serial number/date/type of submission: Original NDA Submission, 28 February, 2000

Information to sponsor: Yes () No (x)

Sponsor (or agent): Pharmacia & Upjohn, 7000 Portage Road, Kalamazoo, MI 49001-0199

Manufacturer for drug substance: Pharmacia and Upjohn

Drug:

Generic Name: Tolterodine tartrate

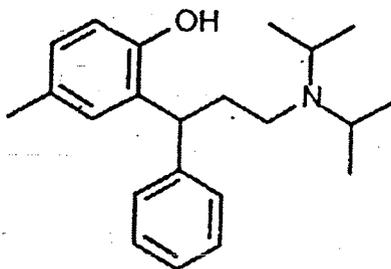
Trade Name:

Chemical Name: (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

CAS Registry Number:

Molecular Formula/ Molecular Weight: $C_{26}H_{37}NO_7$ / 475.6

Structure:



Relevant INDs/NDAs/DMFs: NDA 20-771,

Drug Class: muscarinic receptor antagonist

Indication: overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence

Clinical formulation: capsules containing 2 mg or 4-mg tolterodine tartrate

Layer	Component	Amount per capsule (mg)
Sealcoat polymer layer		
"		
"		
Drug layer	Tolterodine tartrate	
"	Hydroxypropyl methylcellulose	
"		
Prolonged-release polymer layer		
"	Hydroxypropyl methylcellulose	
"		
Overcoat layer	Hydroxypropyl methylcellulose	
"		
Hard gelatin capsule		4 or #3 one

Amount listed is expressed as

† Removed by

Route of administration: oral

Disclaimer -- use of sponsor's material

Introduction and drug history:

Tolterodine tartrate immediate release tablets (Detrol™) were approved for marketing in 1998. The recommended standard dosing regimen is 2 mg twice daily. The new prolonged release formulation has been developed using 2 mg and 4-mg tolterodine L-tartrate, to be given once daily, for convenience.

The immediate release capsule contains 2 mg tolterodine tartrate.

The new clinical formulation is a capsule containing 2 or 4 mg tolterodine tartrate, sugar spheres, (ethylcellulose), hydroxypropyl methylcellulose 2910, and

Comparative pharmacokinetic evaluation in humans of the capsule formulation and the tablet has been stated by the sponsor to show that the AUC_{0-24hr} for both tolterodine and the active metabolite DD01 are about the same for the two formulations; however, the C_{max} is about 60-70 % lower for the release capsule as for the immediate release tablet. The ingredients, except for are listed as GRAS.

In accordance with the ICH guidelines on Impurities in New Drug Products, two *in-vitro* genotoxicity studies and a three month general toxicity study in mice have been performed on the tolterodine degradation products () that may exceed the ICH qualification threshold limit (1%) by the end of the proposed shelf-life of

the capsule. These compounds were synthesized, and reviews of the toxicology studies in which they were evaluated follow.

Studies reviewed within this submission:

Tolterodine and two degradation products
(Gavage Administration) Toxicity Study in the Mouse

): 13 Week Oral
p.4

Bacteria (Ames test)

Gene Mutation Test in
p.7

analysis in human lymphocytes *in vitro*

Metaphase chromosome
p.8

Studies not reviewed within this submission:

Pharmacology and toxicology studies for tolterodine immediate release tablets, reviewed by Alex Jordan, are attached.

**APPEARS THIS WAY
ON ORIGINAL**

TOXICOLOGY:

Study Title: Tolterodine and degradation products
13 Week Oral (Gavage Administration) Toxicity Study in the Mouse

Study No: 1027/415-D6154

Item #5, Vol #1.9, and page #90:

Conducting laboratory and location:

Date of study initiation: 17 February 1999

GLP compliance: yes

QA- Report Yes (x) No ()

Methods:

Dosing:

- species/strain: Crl:CD-1(ICR)BR mice
- #/sex/group or time point: 15/sex/group
- age: 7 weeks
- weight: 28.3-40.9 g (males), 21.5-32.2 (females)
- dosage groups in administered units:

The) were given formulated at
of the amount of Tolterodine)

Three supplementary groups were added to the study due to an error in the preparation of the vehicle and control article used in groups 2 and 5 during Weeks 2 to 4 (a higher concentration of absolute ethanol) than that specified in the protocol [] was used). From Week 5 onward these animals were given doses containing the correct concentration of ethanol. The additional animals were obtained to supplement the animals that received the incorrect vehicle. These additional animals were treated in the same way as the original animals. The deviation was considered not to have affected the outcome or integrity of the study.

Group	Group description and dose levels (mg/kg/day)	A	B	# of Male	# of Female
1	Control [@]	0	0	15	15
2	Tolterodine	10	6.8	15	15
3		0.14+0.16	0.14+0.14	15	15
4	Tolterodine	10+0.14+0.16	6.8+0.14+0.14	15	15
5	Tolterodine +	3+0.04+0.05	2+0.04+0.04	15	15
Supplementary Groups.					
6	Control [#]	0	0	15	15
7	Tolterodine	10	6.8	15	15
8	Tolterodine +	3+0.04+0.05	2+0.04+0.04	15	15

A) expressed as substance supplied

B) expressed as free base

@ In Week 1 the control article was 1% v/v ethanol in purified water. Due to a vehicle preparation error in Weeks 2,3 & 4 the concentration of ethanol was . From Week 5, the concentration was in purified water.

In Week 1 the control article was 1% v/v ethanol in purified water. From Week 2 of treatment onwards the concentration of ethanol was in

- route, form, volume, and infusion rate: oral gavage at 10 ml/kg

Drug:

Test article	lot#	Batch number
Tolterodine L-tartrate	1	ZA18M007
	1	31906-KSF-119-N1
	1	31906-KSF-121-N1
Tolterodine L-tartrate	2	ZA19C004

Results:

- Clinical signs:

Group	Group description and dose levels (mg/kg/day)	A	B	Unscheduled death	
1	Control ^a	0	0	0	0
2	Tolterodine	10	6.8	0	0
3		0.14+0.16	0.14+0.14	2 males	0
4	Tolterodine +	10+0.14+0.16	6.8+0.14+0.14	0	0
5	Tolterodine +	3+0.04+0.05	2+0.04+0.04	2 males	0
Supplementary Groups					
6	Control ^b	0	0	2 males	0
7	Tolterodine	10	6.8	3 males	0
8	Tolterodine +	3+0.04+0.05	2+0.04+0.04	2 males	3 females

- Body weights:

A 20% decrease in body weight gain was seen in females administered tolterodine alone in group 2 and in males administered tolterodine alone in group 7 (35%), compared to control. There were no body weight effects, however, in groups administered the degradation products or both tolterodine and its degradation products, compared to control. No significant differences were observed when groups administered tolterodine plus degradation products were compared to those administered tolterodine alone. Absolute body weights in the tolterodine groups at necropsy did not differ from control by greater than 8%.

- Food consumption: No effects on food consumption were observed.
- Ophthalmoscopy: No treatment related changes were observed.
- Electrocardiography: No treatment related changes were observed.
- Hematology: No treatment related changes were observed.
- Clinical chemistry:

Group description	doses (mg/kg/day)	Urea (male) mmol/L	Urea (female) mmol/L	Creat. (male) μmol/L	Creat. (female) μmol/L	Gluc. (male) mmol/L	Gluc. (female) mmol/L
1 Control	0	10.7+1.6	7.7+0.9	28+2	30+2	5.0+1.2	4.4+0.9
2 Tolterodine	10	10.5+2.1	10.1+1.9*	28+4	34+3*	5.5+0.9	6.8+2.1*
3	0.14+0.16	9.7+1.0	7.7+1.4	27+2	28+2	5.0+1.1	5.9+1.0
4 Tolterodine	10+0.14+0.16	12.0+1.4	9.0+1.4	29+1	28+1	5.4+0.7	6.3+1.5*
5 Tolterodine	3+0.04+0.05	9.9+2.0	7.7+1.2	28+2	28+2	6.8+1.4	6.3+1.4
Supplementary Groups							
6 Control	0	10.8+2.0	9.8+1.7	30+2	32+4	4.4+1.1	6.6+1.8
7 Tolterodine	10	15.2+4.6*	12.3+2.9	31+2	30+3	6.4+1.4*	6.7+1.8
8 Tolterodine	3+0.04+0.05	14.9+3.4	11.3+3.0	30+3	31+3	5.4+1.2	6.1+1.5

- Urinalysis: No treatment related changes were observed.

- Organ Weights: No treatment related changes were observed.
- Gross pathology: No treatment related changes were observed.
- Histopathology: No treatment related changes were observed.
- Toxicokinetics: Not determined. Previous studies in mice have shown that 10 mg/kg/day is about 7 times the blood levels in humans administered 4 mg or 30 times the human dose if measured as the unbound fraction of drug in the blood.

Key Study Findings:

In this study, mice were exposed to tolterodine at mildly toxic blood levels, or to vehicle, degradation product, or one of two concentrations of tolterodine and degradation products. An error in the concentration of vehicle resulted in essential duplication of the control, tolterodine, and higher dose tolterodine plus degradation products groups.

In addition to small changes in body weight which were observed in the tolterodine treatment groups, minor increases in urea, creatinine, and glucose were observed. The addition of degradation products, however, did not significantly increase toxicity above that of tolterodine alone, in any group studied.

**APPEARS THIS WAY
ON ORIGINAL**

Study Title: PNU-200583E in combination with
Mutation Test in Bacteria (Ames test)

Gene

Study No: N1138-Q1655

Study Type: Reverse mutation

Item #5, Volume #1.9 and Page #37

Conducting Laboratory: _____, Pharmacia and Upjohn, _____

Date of Study Initiation/completion: 16 February 1999 / 02 June 1999

GLP Compliance: yes

QA- Reports Yes (x) No ():

Drug Lot Number: PNU-200583E (Batch #ZA18M007, _____) (Batch #31906-KSF-119, _____) (Batch #31906-KSF-121, _____)

Study Endpoint: an increase in the number of revertant colonies

Methodology:

- Strains/Species/Cell line: *Salmonella typhimurium* TA 1535, TA 100, TA1537, and TA98 and *Escherichia coli* uvrA.
- Dose Selection Criteria: Initial study with a high concentration of 5 mg/ml tolterodine plus 100 µg/ml of each degradation product. Cytotoxic doses were not scored or repeated.
- Metabolic Activation System: _____-induced rat liver homogenate fraction S9
- Controls:
 - Vehicle: DMSO
 - Negative Controls: DMSO, 0.1 ml/plate
 - Positive Controls: 2-nitrofluorene (10 µl/plate for TA 98), 9-aminoacridine (70 µg/plate for TA1537), 2-aminoanthracene (5 µg/plate for *S.typhimurium*, 10 µg/plate for *E. coli*), 2-acetylaminofluorene (50 µg/plate for TA98), benzo(a)pyrene (5 µg/plate for TA98 and TA100), sodium azide (5 µg/plate for TA 1535 and TA 100), and methyl methanesulfonate (2.5 µl/plate for *E.coli*)
- Exposure Conditions:
 - Doses used in definitive study: 312.5 + 6.25, 6.25 + 12.5, 1250 + 25, 2500 + 50 and 5000 + 100 µg/ml were used in the first, dose-finding experiment, both in the absence and presence of metabolic activation; 19.53 + 0.39, 39.06 + 0.78, 78.125 + 1.56, 156.25 + 3.125, and 312.5 + 6.25 µg/ml, in the absence of metabolic activation, and 78.125 + 1.56, 156.25 + 3.125, 312.5 + 6.25, 625 + 12.5, and 1250 + 25 µg/ml, in the presence of metabolic activation, were used in the second experiment, based on toxicity observed in the first.
 - Study design: The preincubation method was used. Cultures were preincubated, in the absence or presence of metabolic activation (20 minutes at 37°C), plated, and counted following a 48-hour incubation.
- Analysis:
 - No. slides/plates/replicates/animals analyzed: 2 experiments with 3 plates/group
 - Counting method: automated colony counter
 - Cytotoxic endpoints: a reduction (at least 50%) in the background lawn
 - Genetic toxicity endpoints/results: an increase in the number of revertant colonies

- Statistical methods: test compounds by Dunnett's test and positive controls by Student's t-test

- Criteria for Positive Results: A compound was considered to be mutagenic if it induced a statistically significant increase in the mean number of revertants to at least double that of control, with a dose-response relationship, in two separate experiments.

Results:

- Study Validity: Revertant frequencies in positive and negative controls performed as expected, within the range of historical controls.

- Study Outcome: PNU-200583E in combination with _____ did not induce an increase in the number of revertant colonies over that of the vehicle control at any concentration, in the absence or presence of metabolic activation.

Summary: PNU-200583E (Tolterodine tartrate) in combination with _____ was not genotoxic in this test system.

Study Title: PNU-200583E in combination with _____ chromosome analysis in human lymphocytes *in vitro*

Metaphase

Study No: N1137-Q1654

Study Type: microscopic analysis of chromosome damage in human cells
Item #5, Volume #1.9 and Page #47

Conducting Laboratory: _____ Pharmacia and Upjohn, _____

Date of Study Initiation/completion: 29 January 1999/ 13 October 1999

GLP Compliance: yes

QA- Reports Yes (x) No ():

Drug Lot Number: PNU-200583E (Batch #ZA18M007, _____) (Batch #31906-KSF-119, _____), _____ (Batch #31906-KSF-121, _____)

Study Endpoint: frequency of observable evidence of cytogenetic damage

Methodology:

- Strains/Species/Cell line: human lymphocytes from two donors
- Dose Selection Criteria: Initial study with a high concentration of 1 mg/ml tolterodine plus 20 µg/ml of each degradation product _____. Cytotoxic doses were not scored or repeated.
- Metabolic Activation System: _____ -induced rat liver homogenate fraction S9
- Controls:
 - Vehicle: DMSO
 - Negative Controls: 1% DMSO
 - Positive Controls: mitomycin C (0.1 µg/ml) in the absence of metabolic activation and cyclophosphamide (10 µg/ml) in the presence of metabolic activation
- Exposure Conditions:
 - Doses used in definitive study: 0, 7.8125 + 0.156, 15.625 + 0.3125, 31.25 + 0.625, 62.5 + 1.25, 125 + 2.5 and 250 + 5 µg/ml were used in the first experiment in the 24h-S9 assay. Concentrations above 31.25 + 0.625 µg/ml were not scored

due to toxicity. 0, 31.25 + 0.625, 62.5 + 1.25, 125 + 2.5, 250 + 5, 500 + 10, and 1000 + 20 µg/ml were used in 3+21h-S9+S9 experiment. Concentrations above 125 + 2.5 µg/ml were not scored due to toxicity. 0, 7.8125 + 0.156, 15.625 + 0.3125, 31.25 + 0.625 µg/ml were used in the second experiment for the 48h-S9 exposure and 0, 31.25 + 0.625, 62.5 + 1.25, 125 + 2.5 µg/ml were used for the 45+3h+S9 exposure.

- Study design: Lymphocytes were incubated 3 hours followed by 21 hours of recovery (3+21h) and 24 hours (24h) in the test without metabolic activation (-S9), and 3 hours followed by 21 hours of recovery (3+21h) in the test with metabolic activation (+S9), in the first experiment. In the second experiment, they were incubated 48 hours (48h) in the test without metabolic activation (-S9), and 3 hours followed by 45 hours of recovery (3+45h) in the test with metabolic activation (+S9).

- Analysis:

- No. slides/plates/replicates/animals analyzed: Four slides per culture were examined. For each culture 100 euploid metaphases were examined microscopically (25 per slide). Metaphases with 45 chromosomes were also scored if they showed aberrations.

- Cytotoxic endpoints: reduction of the mitotic index to 50 – 80 % of that of the vehicle control

- Genetic toxicity endpoints/results: chromosome- and chromatid-type aberrations (breaks, fragments, minutes, rings, and interchanges)

- Statistical methods: Fisher's exact test, two-tailed

- Criteria for Positive Results: The test compound was considered clastogenic if at least two consecutive concentrations induced a statistically significant increase, compared to controls, in the frequency of aberrant chromosomes in the lymphocytes of two donors, separately and pooled.

Results:

- Study Validity: Positive and negative controls performed as expected, within the range of historic in-house and published controls.

- Study Outcome: None of the concentrations of PNU-200583E in combination with its degradation products, scored for analysis induced statistically significant increases in the frequency of aberrant cells compared to the vehicle control ($P < 0.05$ by Fisher's exact test) in the presence or absence of metabolic activation, at any of the sampling times tested.

Summary: PNU-200583E (Tolterodine tartrate) in combination with its degradation products, was not genotoxic in this assay.

Overall Toxicology Summary:

No new toxicity was identified for tolterodine degradation products.

Addendum list:

Addendum 1
Histopathology Inventory for IND #

Study	1027/415 -D6154			
Species	mouse			
Adrenals	X			
Aorta	X			
Bone Marrow smear	X			
Bone (femur)	X			
Brain	X*			
Cecum	X			
Cervix				
Colon	X			
Duodenum	X			
Epididymis	X*			
Esophagus	X			
Eye	X			
Fallopian tube				
Gall bladder	X			
Gross lesions	X			
Harderian gland	X			
Heart	X*			
Hypophysis				
Ileum	X			
Injection site				
Jejunum	X			
Kidneys	X*			
Lachrymal gland	X			
Larynx	X			
Liver	X*			
Lungs	X*			
Lymph nodes, cervical				
Lymph nodes mandibular	X			
Lymph nodes, mesenteric	X			
Mammary Gland	X			
Nasal cavity	X			
Optic nerves	X			
Ovaries	X			
Pancreas	X			
Parathyroid	X			
Peripheral nerve	X			
Pharynx	X			
Pituitary	X			
Prostate	X			
Rectum	X			
Salivary gland	X			
Sciatic nerve	X			
Seminal vesicles	X			
Skeletal muscle	X			
Skin	X			
Spinal cord	X			
Spleen	X*			
Sternum	X			
Stomach	X			
Testes	X*			
Thymus	X			
Thyroid	X			
Tongue	X			
Trachea	X			
Urinary bladder	X			
Uterus	X			
Vagina	X			
Zymbal gland	X			

* organ weight obtained

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

Memo from DSI regarding GLP inspection

Not applicable for this submission.

**APPEARS THIS WAY
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NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

Statistical review(s) of carcinogenicity studies

Not applicable for this submission.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

CAC/ECAC report

Not applicable for this submission.

**APPEARS THIS WAY —
ON ORIGINAL**

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

Abuse Liability Review

Not applicable for this submission.

**APPEARS THIS WAY
ON ORIGINAL**

NDA 21-228
Tolterodine extended release capsules
Pharmacia & Upjohn Company

Microbiology Review

Not applicable for this submission.

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