Clinical Pharmacology and Biopharmaceutics Review

NDA	21,228/20,771
Submission Date	October 10, 2003
Brand Name	Detrol and Detrol LA
Generic Name	Tolterodine tartrate
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Pfizer
Submission Type; Code	Pediatric Exclusivity Submission; 3S
Dosing regimen	Daily or BID

Executive Summary

NDAs 21,228 and 20,771 are currently approved for urge urinary incontinence in adults at doses of 1 and 2 mg immediate release (IR) and 2 and 4 mg modified release (MR). Pfizer was issued a written request to conduct pediatric studies using tolterodine, dated January 23, 2001. The sponsor conducted 2 pharmacokinetic (PK)/safety studies, 3 pharmacokinetic/pharmacodynamic (PK/PD) studies and 2 phase 3 safety and efficacy trials. Additionally, since a non-marketed liquid was used in the younger children, 2 bioequivalence (BE) studies were also performed. The following table summarizes the submitted studies.

Study #	Study/Analysis Type	Design	Age	Dose/Dosage Form
018	PK and Safety Study	Open label, non-controlled, multiple dose, dose escalation	11-15 years	2 and 4 mg QD, prolonged release (MR) capsules
044	PK and Safety Study	Open label, non-controlled, multiple dose, dose escalation	5-10 years	0.5, 1, and 2mg BID immediate release (IR) tablet
001	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	1 month – 4 years	0.030, 0.060 and 0.120 mg/kg/day (BID), IR liquid preparation
002	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	5-10 years	0.030, 0.060 and 0.120 mg/kg/day (BID), IR liquid preparation
003	Phase 1/2 PK/PD Study	Open label, non-controlled, multiple dose, dose escalation	11-15 years	2 and 4 mg QD, MR capsules
008	Phase 3 Efficacy and Safety	Randomized, double blind, multicenter	5-10 years	2 mg QD, MR capsules
020	Phase 3 Efficacy and Safety	Randomized, double blind, multicenter	5-10 years (higher baseline micturitions than Study 008)	2 mg QD, MR capsules
018 and 044	Population-PK Analysis	Pooled population analysis of data from studies 018 and 044	5-15	See Study 018 and 044 descriptions above
018, 044, 008 and 020	Population-PK Analysis	Using the previously developed model, analysis of sparse sampling data from studies 008 and 020	5-15	See Study 018, 044, 008 and 020 descriptions above
004	Relative Bioavailability Study	open, randomized, 3-way, single-dose, crossover, PK study	Adults	2 different liquid IR solutions and tolterodine IR tablets
005	Relative Bioavailability Study	open, randomized, 2-way, single-dose, crossover, PK study	Adults	Opened MR capsules over applesauce and intact MR capsules

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the information included in the sNDA and has found that the

pharmacokinetics of tolterodine in children was adequately characterized; however, tolterodine use was not shown to be effective in the pediatric population.

Summary of Clinical Pharmacology/Biopharmaceutics Findings

Metabolism

Tolterodine is metabolized by CYP2D6 to active metabolite DD01 in extensive CYP2D6 metabolizers (EM) and metabolized by CYP3A4 to assorted inactive metabolites in poor CYP2D6 metabolizers (PM). Both tolterodine and DD01 have equal binding affinities to muscarinic receptors and lead to equal muscarinic receptor antagonism. As such, the sponsor defines the active moiety as the sum of the unbound tolterodine and DD01.

Pharmacokinetics

Two PK/safety trials were submitted for review. Study 044 (N=30, 28 EM, 2 PM) studied the safety and PK 0.5, 1, 2 and 3mg BID for 14 days of a non-marketed IR liquid preparation in 5-10 year olds. Study 018 (N=29, 27 EM, 2 PM) studied the safety and PK of 2 and 4mg QD for 6-10 days of the MR (Detrol LA) formulation.

Study 044 showed linear active moiety exposures over the dose range studied. According to the achieved exposures, 1 mg BID (IR liquid) in 5-10 year old children yields active moiety exposures similar to that achieved with standard 2 mg BID (IR tablets) dosing in adults. Distinction between the non-marketed IR liquid and IR tablets is made because the two preparations did not meet bioequivalence criteria (Study 004).

Study 018 also showed linear active moiety exposures over the dose range studied. In 11-15 year old children, 4 mg QD of the MR formulation yielded active moiety exposures similar to that achieved with the same dose/formulation in adults. However, these results were confounded by the fact that some children in the study, those with trouble swallowing the capsule, emptied the contents of the capsule over applesauce and ingested it instead of taking the capsule intact. Although the sponsor assumed these administration routes were bioequivalent, they in fact did not meet bioequivalence criteria in Study 005, a study conducted in adults to test the bioequivalence of intact and opened MR capsules.

Most adverse events noted are those consistent with muscarinic antagonism.

PK/PD

Three PK/PD studies were submitted for review. Studies 001, 002 and 003 were open label, non-controlled, multiple-dose, dose escalation studies in children with neurogenic disease. Studies 001 and 002 studied dose-response, using the non-marketed IR liquid, in children 3 month to 4 years of age and 5 to 10 years of age, respectively. Study 003 studied dose-response in 11 to 15 year old children using the MR formulation.

In all three studies, analysis of mean data suggested some dose-response relationship in several of the urodynamic variables that were measured, as seen below (Study 001).

Urodynamic Data; Study 001 (N=19)

Dose Period	Statistic	Volume to first detrusor contraction of magnitude >10 cm H_2O pressure (mL)	Functional bladder capacity (mL)	Leak point pressure (cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)
	Median (min-max)	15.0 (4.0 to 60.0)	62.0 (13.0 to 160.0)	48.0 (12.0 to 90.0)
	Not reported	0	0	0
Period 1: 0.030 mg/kg/day	Mean (SD)	25.5 (22.9)	70.7 (33.5)	50.5 (29.3)
	Median (min-max)	22.0 (3.0 to 71.0)	73.0 (15.0 to 136.0)	47.0 (10.0 to 113.0)
	Not reported	2	0	1
Period 2: 0.060 mg/kg/day	Mean (SD)	38.9 (29.7)	101.6 (67.5)	40.9 (21.4)
	Median (min-max)	31.5 (5.0 to 123.0)	87.0 (19.0 to 278.0)	40.0 (12.0 to 81.0)
	Not reported	3	1	3
Period 3: 0.120 mg/kg/day	Mean (SD)	56.9 (67.5)	100.4 (71.1)	42.6 (27.9)
	Median (min-max)	20.0 (10.0 to 232.0)	68.0 (24.0 to 238.0)	32.0 (13.0 to 101.0)
	Not reported	2	2	5
Change from baseline to period 1	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)
	Median (min-max)	1.0 (-26.0 to 49.0)	-16.0 (-73.0 to 70.0)	0.0 (-44.0 to 53.0)
	H-L (95% C.I.)*	0.5 (-9.0, 13.0)	-3.0 (-23.0, 16.0)	0.5 (-8.0, 8.5)
	Not reported	2	0	1
Change from baseline to period 2	Mean (SD)	15.9 (30.5)	31.7 (54.7)	-8.4 (14.4)
	Median (min-max)	11.0 (-29.0 to 91.0)	28.5 (-41.0 to 182.0)	-7.0 (-40.0 to 12.0)
	H-L (95% C.I.)*	15.0 (-1.5, 33.0)	24.0 (1.5, 54.5)	-7.0 (-16.5, 0.0)
	Not reported	3	1	3
Change from baseline to period 3	Mean (SD)	34.4 (61.4)	32.5 (63.7)	-3.0 (14.3)
	Median (min-max)	10.0 (-34.0 to 213.0)	9.0 (-36.0 to 176.0)	-1.5 (-27.0 to 20.0)
	H-L (95% C.I.)*	20.0 (1.5, 59.0)	21.0 (-5.0, 69.0)	-3.0 (-12.0, 6.0)
	Not reported	2	2	5

However, large confidence intervals suggested highly variable results. Examination of the individual data in all three studies failed to show any consistent dose-response relationship. The following figure examines the dose-response in the subjects of Study 001 and is representative of the dose-response relationship seen in all three studies.

Change from Baseline in Volume to First Detrusor Contraction; Individual Data from Study 001 (N=19)

(b)(4)

This disparity between mean and individual results was generally caused by a small number of outliers (2-3) per treatment group that led to a skewing of the mean results.

Safety and Efficacy
The sponsor performed two phase 3 safety and efficacy trials. In both studies, no efficacy was demonstrated in treating 5-10 year olds with urge urinary incontinence with 2 mg daily of the MR formulation. For more information relevant to these studies, the reader is referred to the detailed medical review.

Population PK Analyses
Two population PK analyses were submitted by the sponsor. The first analysis involved modeling parent and metabolite concentrations using the data rich PK studies, 044 and 018. A three compartment model best fit the data. The following covariates were identified as contributing to the PK of tolterodine and DD01 in children; 2D6 phenotype, weight, height, gender, $alpha_1$ acid glycoprotein (AGP) and formulation/age. The last covariate's designation reflects the fact that the effect of age cannot be separated from the effect of formulation in this dataset because younger children were treated with the IR formulation and older children were treated with the MR formulation in Studies 018 and 044. Also age, weight, height and sex were found to be highly correlated.

The second analysis involved fitting the sparse PK data from the two phase 3 trials to the previously developed model. The new data allowed partial separation of the variables of age and formulation and found race also plays a significant role in the PK characteristics of tolterodine and DD01. Further analysis of the phase 3 data suggests that mean active moiety AUC was lower than that achieved in adults.

This lower observed exposure may have resulted from some assumptions made by the sponsor in the tolterodine pediatric development program. The sponsor assumed that the IR liquid used in the PK studies would result in similar exposures to that achieved with the same dose of the IR tablet. They also assumed that children would, like adults, experience similar active moiety exposures at a stable dose of tolterodine, whether administered in the IR or MR formulation. That stable dose/formulation/exposure relationship has not been demonstrated in children.

Overall Conclusion
In the following pediatric development process the sponsor selected doses to study in children based on an assumption that drug exposures associated with effective doses in adults would yield efficacy in the pediatric population. The sponsor conducted initial pediatric PK studies to determine the dose that yielded these adult exposures, but subsequent PK/PD studies in children did not show a response and no efficacy was demonstrated in 2 Phase 3 trials.

The doses selected for testing efficacy in the 2 phase 3 trials might have been different had the sponsor first performed PK/PD studies to determine the exposure associated with adequate response and then performed PK studies to determine the dose in children required to achieve these exposures. The efficacy data, however, that were presented in this application do not support use of tolterodine for treatment of children.

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