NDA 21-228 – SE-8 supplement 006

BPCA Clinical Review

Drug: Detrol LA Capsules (tolterodine tartrate)

1.0 Brief Background:

Detrol LA is currently approved in adults for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. NDA 21-228 (supplement 006) contains pediatric efficacy and safety studies including pharmacokinetic data and proposed labeling in response to a written request for pediatric studies to be performed in both neurologically impaired and neurologically normal children. The submission contains no new CMC or pharmacology/toxicology information. The Pediatric Exclusivity Board met on January 5, 2004, and granted an additional 6-month exclusivity for both NDA 21-228 (Detrol LA) and NDA 20-771 (Detrol).

2.0 Executive Summary and Recommendation:

Based on the clinical and pharmacokinetic data submitted in response to a Pediatric Written Request, this supplement may be **approved**. Efficacy was not demonstrated in either the neurologically impaired or neurologically normal pediatric patient populations. New safety information from the pediatric studies should be incorporated into the Detrol LA label.

3.0 Overview of Submitted Efficacy and Safety Studies:

In response to the written request, the sponsor submitted the results of 3 studies in neurologically impaired children (001, 002, and 003), 2 studies in neurologically intact children with symptoms of urgency incontinence (008 and 020), and an open-label extension safety study (021) containing subjects from Studies 020 and 018. In addition, 2 pharmacokinetic (PK) studies (018 and 044) and two bioequivalence studies (004 and 005) were submitted.

Studies in neurologically impaired children:

Study #	N	age	formulation	dose	placebo
001	19	1 mo-4yrs	syrup	0.03, 0.60, 0.12 mg/kg/day	no
002	15	5-10 yrs	syrup	0.03, 0.60, 0.12 mg/kg/day	no
003	11	11-15 yrs	Detrol LA	2, 4, 6 mg/day	no

Studies in neurologically intact children:

Study #	N	Age	Formulation	Dose	Placebo
008	369	5-10 yrs	Detrol LA	2 mg/day	Yes Drug:plac = 2:1
020	342	5-10 yrs	Detrol LA	2 mg/day	Yes Drug:plac = 2:1

4.0 Studies in neurologically impaired children

The trial designs of the 3 studies (001, 002, and 003) in neurologically impaired patients were nearly identical except for the ages of the patients and the formulations studied.

Studies 001 and 002 were 12 week, multicenter, open-label, dose escalation, PK, pharmacodynamic (PD), clinical efficacy and safety studies. Patients were enrolled within 3 months of a baseline urodynamic evaluation. In 001 and 002, dosing was initiated at 0.03 mg/kg/day in two divided doses and maintained for four weeks. Following review of the safety data, the dose was escalated to 0.06 mg/kg/day for four weeks and then to 0.12 mg/kg/day for four weeks. Urodynamic data, patient diary data, and safety data were collected at the end of each dose period. PK data were collected only at the 0.06 mg/kg/day dose. The drug formulation used in Trials 001 and 002 was an investigational product, tolterodine tartrate oral solution (1 mg/5 cc) which is not commercially available. The mid-range dose (0.06 mg/kg/day) was chosen to approximate the exposure of adults receiving 2 mg bid of the tolterodine IR tablet. In study 003 (10 to 15 year-old group), all patients received Detrol LA 2 mg for 4 weeks, then 4 mg for 4 weeks, and finally 6 mg for 4 weeks. Patients enrolled in Trial 003 who were unable to swallow the capsule(s) were allowed to empty the capsule and consume the beads sprinkled over food.

Inclusion criteria included patients with stable neurological disease (meningomyelocoele, spinal dysraphism, cerebral palsy, traumatic spinal cord injury) and urodynamic evidence of detrusor hyperreflexia. Patients were required to need intermittent catheterization for management of urinary drainage. Exclusion criteria included use of an indwelling cathether within 4 weeks of enrollment, clinically significant urinary tract infection, and treatment with a potent CYP 3A4 inhibitor within 7 days of any study measurements.

Endpoints included both data obtained from urodynamic evaluation and data derived from patient diaries. Urodynamic endpoints were: 1) volume to first detrusor contraction of > 10 cm H_20 pressure 2) functional bladder capacity and leak point pressure 3) intravesical volume at 20 and 30 cm H_20 pressure 4) maximal cystometric capacity (intravesical volume at 40 cm H_20 pressure) 5) bladder compliance and 6) percent change in cystometric capacity. Diary derived endpoints were: 1) mean number of catheterizations or micturitions per 24 hours 2) mean volume per catheterization/micturition and 3) mean number of incontinence episodes/24 hours. Diary data were based on means derived from three-day diary recordings done at baseline and at each dose period (weeks 4, 8, and 12).

4.1 Trial 001 (Drug formulation is syrup):

Nineteen patients (10 boys and 9 girls) were enrolled. More than 80% were Caucasian. Three patients were less than 6 months of age, 6 were between 6 months and 2 years, and 10 were between 2 and 4 years of age. Eighteen patients had myelomeningocele and one had experienced a spinal cord injury.

Changes from baseline in urodynamic measurements are shown in Table 1.

Table 1. Study 001 Change from baseline urodynamic variables

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	21.7 (16.6)	74.2 (41.5)	49.0 (21.3)	42.6 (21.1)	50.9 (30.8)	71.3 (43.6)	2.1 (1.1)	1.7 (1.0)	1.8 (1.1)
	N	19	19	19	19	13	12	19	13	12
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	2.5 (20.9)	-3.5 (36.6)	0.4 (20.8)	2.4 (28.6)	-3.2 26.4)	-10 (36.0)	0.1 (1.4)	-0.1 (0.9)	-0.3 (0.9)
	N	17	19	18	18	12	9	18	12	9
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	15.9 (30.5)	**31.7 (54.7)**	-8.4 (14.4)	**37.1 (52.2)**	24.1 (45.7)	46.0 (74.0)	**1.9 (2.6)**	0.8 (1.5)	1.2 (1.8)
	N	16	18	16	14	8	6	14	8	7
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**34.4 (61.4)**	32.5 (63.7)	-3 (14.3)	**29.2 (46.9)**	27.2 (59.5)	12.8 (40.1)	**1.5 (2.3)**	0.9 (2.0)	0.3 (1.0)
	N	17	17	14	15	9	5	15	9	5

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary data (Trial 001) are shown in Table 2.

Table 2. Study 001 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	4.8 (1.4)	5.2 (1.9)	34.9 (16.1)
	N	18	18	18
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	-0.1 (1.1)	-0.2 (2.0)	5.7 (19.9)
	N	18	18	18
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.2 (1.1)	**-0.9** **(1.9)**	**13.2** **(24.0)**
	N	17	18	17
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.1 (0.8)	**-1.2** **(1.7)**	**21.7** **(25.7)**
	N	16	17	16

Bold cells – Confidence interval around the change from baseline does not contain 0

4.2 Trial 002 (Drug formulation is syrup):

Fifteen patients (7 boys and 8 girls) were enrolled. Seven patients were between 5 and 7 years of age, inclusive, and 8 were between 8 and 10 years, inclusive. Greater than 70% of the patients were Caucasian. Nine patients had myelomeningocele, 2 had spinal cord injury, and the remainder are listed as having a congenital spinal cord anomaly.

Changes from baseline in urodynamic parameters are shown in Table 3.

Table 3. Study 002 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	38.4 (40.7)	119.7 (57.4)	45.6 (12.8)	58 (59.2)	81.3 (69.3)	88.7 (66.4)	2.9 (3.0)	2.7 (2.3)	2.2 (1.7)
	N	14	15	12	13	10	6	13	10	6
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	**26.7 (40.3)**	37.2 (69.8)	0 (8.4)	26.9 (73.8)	**65.3 (44.4)**	21.8 (31.7)	1.3 (3.7)	**2.2 (1.5)**	0.5 (0.8)
	N	**11**	14	10	11	7	4	11	7	4
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	**29.6 (42.3)**	40.7 (82.0)	13.3 (28.6)	**35.2 (38.2)**	33.9 (41.6)	49 (120.0)	**1.8 (1.9)**	1.1 (1.4)	1.2 (3.0)
	N	**12**	14	8	**10**	8	4	**10**	8	4
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	**37.0 (55.9)**	65.0 (101.0)	2.6 (17.6)	**38.3 (83.6)**	53.1 (90.6)	86.2 (94.4)	**1.9 (4.2)**	1.8 (3.0)	2.2 (2.4)
	N	12	13	8	12	9	6	12	9	6

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary variables are shown in Table 4.

Table 4. Study 002 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	4.7 (1.4)	4.3 (1.0)	88.8 (45.9)
	N	15	14	15
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	0 (0.8)	**-0.6** **(0.8)**	7.8 (25.7)
	N	15	14	15
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.1** **(1.3)**	6.2 (25.3)
	N	14	13	14
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.1 (1.1)	**-1.3** **(1.3)**	18.9 (30.7)
	N	13	13	13

Bold cells – Confidence interval around the change from baseline does not contain 0

4.3 Trial 003 (Drug formulation is extended release capsule, Detrol LA):

Eleven patients (5 boys and 6 girls) were enrolled. Greater than 70% were Caucasian. Eight patients were between 11 and 13 years of age, inclusive, and 3 were between 14 and 15 years of age, inclusive. Eight patients had myelomeningocele, two are listed as having a congenital spinal cord anomaly, NOS, and one patient's diagnosis was unspecified.

Changes from baseline in urodynamic variables are shown in Table 5.

Table 5. Study 003 Change from baseline in urodynamic measurements

		VFDC (ml)	FBC(ml)	LPP (cm H_2O)	IVV at 20 cm H_2O (ml)	IVV at 30 cm H_2O (ml)	IVV at 40 cm H_2O (ml)	BWC 0-20 cm H_2O (ml/cm H_2O)	BWC 0-30 cm H_2O (ml/cm H_2O)	BWC 0-40 cm H_2O (ml/cm H_2O)
Baseline	Mean (SD)	132.4 (76.7)	232.0 (62.7)	33.9 (15.1)	150.1 (95.4)	153.6 (47.6)	197.7 (49.0)	7.5 (4.8)	5.1 (1.6)	4.9 (1.2)
	N	11	11	9	9	5	3	9	5	3
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	25.9 (107.6)	**79.1 (90.8)**	2.0 (19.8)	72.8 (104.2)	143.7 (102.9)	134.5 (74.2)	3.6 (5.2)	4.8 (3.4)	3.4 (1.9)
	N	10	11	7	8	3	2	7	3	2
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	35.0 (59.4)	-3.8 (71.8)	5.8 (14.2)	56.0 (82.1)	22.8 (36.6)	-77.0 (28.3)	2.8 (4.1)	0.8 (1.2)	-1.9 (0.7)
	N	8	9	5	7	4	2	7	4	2
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	18.9 (114.4)	**59.4 (67.0)**	-6.4 (19.1)	45.6 (67.9)	**67.8 (61.7)**	54.0 (111.7)	2.3 (3.4)	**2.3 (2.1)**	1.4 (2.8)
	N	8	10	5	7	4	2	7	4	2

VFDC= Volume to first detrusor contraction > 10 cm H_2O

FBC = Functional bladder capacity

LPP = Leak point pressure

IVV= Intravesical volume

BWC= Bladder wall compliance

Bold cells – Confidence interval around the change from baseline does not contain 0

Changes from baseline in micturition diary variables are shown in Table 6.

Table 6. Study 003 Change from baseline in micturition diary variables

		Mean # catheterizations or micturitions per 24 hours	Mean # incontinence episodes per 24 hours	Mean volume per catheterization or micturition (ml)
Baseline	Mean (SD)	5.4 (1.9)	2.4 (1.8)	131.9 (48.8)
	N	11	11	11
Change from Baseline to Dose 1 (0.03 mg/kg/day)	Mean (SD)	-0.3 (0.9)	**-0.6** **(0.6)**	38.4 (60.4)
	N	11	**11**	11
Change from Baseline to Dose 2 (0.06 mg/kg/day)	Mean (SD)	-0.7 (2.0)	**-0.9** **(0.9)**	**34.3** **(30.9)**
	N	9	**9**	9
Change from Baseline to Dose 3 (0.12 mg/kg/day)	Mean (SD)	-0.9 (2.0)	**-0.7** **(0.8)**	38.5 (66.5)
	N	10	10	10

Bold cells – Confidence interval around the change from baseline does not contain 0

4.4 Comment:

Trials 001, 002, and 003 (the 3 trials in neurologically impaired children) were small, non-randomized, and not placebo controlled.

The urodynamic data from Trials 001, 002, and 003 were inconsistent across and within studies. While there were some individual variables in the two studies using tolterodine syrup that showed an apparent favorable change from baseline at some doses, only volume to first detrusor contraction, intravesical volume at 20 cm H_20, and bladder wall compliance from 0-20 cm H_20 showed a dose-response trend, and that was seen only for Study 001, which evaluated the youngest patient population.

In Trials 001, 002, and 003, there were suggestions of improvement in the number of incontinence episodes. In the 2 trials using tolterodine syrup (001 and 002), the urinary volume per micturition tended to increase at higher doses, although a dose-response trend was seen only in Study 001, which evaluated the youngest population (0-4 years). Interpretation of trends is hampered by the lack of a placebo control group.

No clear relationships between the total daily dose (by mg or by mg/kg) administered of tolterodine extended release capsules or tolterodine syrup and the PK results in pediatric patients with neurologic disease were identified.

No clear dose-response or concentration-response relationships between the dose administered of tolterodine extended release capsules or tolterodine syrup and pharmacodynamic results in pediatric patients with neurologic disease were identified.

In summary, the efficacy of tolterodine was not demonstrated in the pediatric population of neurologically impaired patients. There was a lack of consistent effect and a general lack of dose-response trends across the 3 non-randomized, non-placebo controlled studies.

5.0 Neurologically intact children

Trials 020 and 008 were randomized controlled trials that studied the effects of Detrol LA in neurologically normal children aged 5 to 10. Trial 020 was a multinational, multicenter, randomized, double-blind, placebo-controlled, 12 week treatment duration study in children with symptoms of urinary urge incontinence suggestive of detrusor instability. Patients were randomized to either Detrol LA at a fixed 2 mg/day dose or placebo in a 2:1 ratio. The Detrol LA dose was chosen after comparison of the PK of tolterodine and DD01 (the active metabolite) in children aged 5 to 10 years with adults showed that a daily total of 2 mg tolterodine immediate release in children produced exposure equivalent to that seen in adults taking a total daily dose of 4 mg tolterodine IR (both dosed bid). If the child were unable to swallow the capsule, it was opened and the beads were taken with food.

Efficacy data (diary data) were collected twice (at baseline and at week 12) for a seven-day period. Upon completion of the study, patients were eligible to enter a 12 month open label safety extension study. Unlike the trials in the neurologically impaired children, no urodynamic evaluation was performed in this trial.

Inclusion criteria included: male or female, aged 5 to 10 years inclusive, with symptoms of urinary urge incontinence suggestive of detrusor instability, defined as one or more episodes of incontinence or dampness daily during waking hours for at least 5 of 7 days, as confirmed by the run-in micturition chart.

Exclusion criteria included: 1) nocturnal enuresis or "giggle incontinence" or overactive bladder of neurologic origin 2) fewer than 2 micturitions/day during the run-in charting period 3) UTI at Visit 1, a history of urinary retention, or PVR >20% of theoretical bladder capacity on at least 2 bladder scans at Visit 2 4) severe constipation not responding to oral treatment and 5) post-menarchal females.

Trial 008 was similar in design to Trial 020, except that efficacy data (diary data) were collected at baseline and after both 4 and 12 weeks of treatment. The inclusion criteria also included a mean urinary frequency of 6 or more micturitions per 24 hours, as confirmed by the run-in micturition chart. Female patients had to be abstinent or use adequate contraception for three months prior to Visit 2 and throughout the study. Menstruating females underwent a urine pregnancy test. Like Trial 020, the study medication was Detrol LA 2 mg/day.

Efficacy results:

5.1 Trial 020:

In Trial 020, 342 patients were enrolled, with a slight male plurality. Over 90% were Caucasian. In the 5-7 year old group there were 55 placebo and 123 tolterodine treated patients; in the 8-10 year old group there were 52 placebo and 112 tolterodine treated patients.

The primary endpoint in Trial 020 was change from baseline to week 12 in the number of weekly incontinence episodes during waking hours. These efficacy results are shown in Table 7.

Table 7. Change in Weekly Incontinence Episodes

Number of Incontinence Episodes/Week	Treatment Group	
	Placebo (n = 107)	**Tolterodine PR 2 mg q.d. (n = 235)**
Missing	1	1
Baseline		
Mean (SD)	13.8 (8.0)	14.2 (9.3)
Median (min – max)	12.0 (4.0 to 46.2)	11.4 (0.0 to 60.0)
Week 12		
Mean (SD)	10.0 (8.7)	8.9 (9.1)
Median (min – max)	8.0 (0.0 to 47.0)	7.0 (0.0 to 63.0)
Change from baseline to Week 12		
Mean (SD)	-3.8 (6.1)	-5.3 (7.6)
Median (min – max)	-3.0 (-23.2 to 16.3)	-4.7 (-60.0 to 13.0)
p-value	<0.0001	<0.0001
Treatment difference		
Estimated difference in mean change (SEM)	-1.54 (0.84)	
95% confidence interval	-3.19, 0.12	
p-value	0.0689	

ITT = intent to treat; LOCF = last observation carried forward; max = maximum; min = minimum; PR = prolonged release; q.d. = once daily; SD = standard deviation; SEM = standard error of the mean.

The change from baseline was significant in both the tolterodine and the placebo arms. Comparison of the tolterodine and placebo groups, however, did not show a statistically significant difference.

The secondary endpoint, number of micturitions per 24 hours, data were not reported for the entire ITT group; rather, a subgroup analysis based on urinary frequency at baseline (7 or fewer micturitions/24 hours vs. greater than 7/24 hours) was performed. Results were not significant in either subgroup.

5.2 Trial 008:

In Trial 008, 369 patients were enrolled, with a slight male plurality. Over 90% were Caucasian. In the 4-6 year old group there were 100 tolterodine and 55 placebo treated patients, in the 7-8 year old group 106 tolterodine and 40 placebo patients, and in the 9-11 age group 46 tolterodine and 22 placebo patients.

The primary efficacy endpoint was change from baseline to week 12 in number of weekly incontinence episodes during waking hours. These efficacy results are shown in Table 8.

Table 8. Change in Weekly Incontinence Episodes

Number of Daytime Incontinence Episodes per Week		Tolterodine PR 2 mg qd (N = 252)	Placebo (N = 117)
Baseline	Mean (SD)	19.39 (13.31)	18.82 (14.07)
	Median (min – max)	16.00 (2.00 – 85.00)	14.00 (4.67 – 84.00)
	Patients not reporting (n)	1	0
Week 4	Mean (SD)	11.91 (12.71)	13.31 (12.94)
	Median (min – max)	8.00 (0.00 – 101.00)	11.00 (0.00 – 74.00)
	Patients not reporting (n)	0	0
Week 12	Mean (SD)	9.34 (11.78)	10.03 (10.06)
	Median (min – max)	5.00 (0.00 – 98.00)	7.00 (0.00 – 62.00)
	Patients not reporting (n)	0	0
Change from baseline to Week 12	Mean (SD)	–10.02 (12.15)	–8.79 (11.13)
	Median (min – max)	–9.00 (–76.00 – 18.00)	–7.00 (–49.00 – 19.00)
	Patients not reporting (n)	1	0
Difference vs. placebo after 12 weeks	Least Square Mean (SEM)	–0.88 (1.05)	
	95% CI	(–2.94, 1.18)	
	p-value	0.403	

Comparison of the change from baseline of tolterodine vs. placebo showed no statistical significance.

Mean number of daily micturitions was a secondary endpoint. The changes in mean number of daily micturitions at either week 4 or 12 were not significantly different between treatment and placebo groups.

5.3 Summary of Randomized Controlled Trials of Detrol LA in Neurologically Normal Patients with Urgency Incontinence

In children with urinary urge incontinence, statistically significant change from baseline in the primary efficacy endpoint, number of weekly daytime incontinence episodes, was not demonstrated in either Trial 020 or 008. The change in mean number of daily micturitions was not significantly different between treatment and placebo groups. Since only one dose was evaluated in these children, dose-response relationships could not be assessed.

6.0 Safety Summary

6.1 Safety Data from Submitted Trials

Safety data from eight submitted pediatric trials were reviewed. Additional information submitted by the sponsor was also reviewed, including the 2003 Annual Report and final study reports of Study 007 and 009, which were ongoing at the time of the NDA submission. Study 007 was an open-label, uncontrolled safety and efficacy study of tolterodine immediate release solution in children aged 5-10 years with urinary frequency and urge incontinence (N=142). Study 009 was a 12-month safety extension study of Study 008 (N = 318).

The database from these pediatric trials includes 1577 patients of whom 1353 were exposed to tolterodine. Only 2 of the trials (008 and 020) were placebo-controlled. Since the doses

administered did not show efficacy, the safety database may underestimate adverse events if higher doses of tolterodine are administered to children.

There were no deaths in any of the trials. Among all submitted pediatric studies, there were a total of 26 serious adverse events (SAEs) occurring in 22 subjects, 12 of which occurred in the two 12-month extension studies (021 and 009). Two of the trials included a placebo group; only two of the placebo subjects experienced an SAE. Only the 2 placebo subjects with SAE's were discontinued from the study due to the serious adverse event and the only SAE considered by the sponsor to be treatment-related was a case of pyelonephritis in a placebo patient. Reported SAE's included four urinary tract infections (UTIs), all in tolterodine-treated children, four cases of pyelonephritis, one of which was in a placebo-treated subject, and a variety of injuries and infections. With the exception of the eight cases of upper and lower tract UTI's and one case of seizures, the reviewer agrees with the sponsor that these events are unlikely to be related to tolterodine.

In the two placebo-controlled trials, events that occurred with at least twice the frequency in tolterodine vs. placebo-treated subjects were diarrhea, constipation, ear infection, abnormal behavior and rhinitis. Although not occurring at twice the placebo rate, the elevated frequency of UTIs is notable (6.6 % in subjects treated with tolterodine, 4.5% in subjects who received placebo). UTIs occurred in every study except the two studies that were of less than two weeks duration. The increase seen over placebo-treated subjects suggests that treatment with tolterodine may increase the risk of UTI. Tolterodine-treated patients had a minor increase in post-void residual urine volume; possibly this is sufficient to lead to UTI in susceptible children.

Across all pediatric trials, a total of 18 subjects manifested aggressive and/or abnormal behavior while on tolterodine. Although behavioral problems may be associated with urinary incontinence, examination of the placebo-controlled trials allows evaluation of a homogeneous population, differing only in their exposure to tolterodine. In these trials, nine tolterodine-treated patients experienced aggressive or abnormal behavior. By comparison, only one placebo subject experienced such behavior. In six tolterodine subjects, the behavior was marked enough to cause withdrawal from the trial.

6.2 Safety Information from AERS Database

In addition to the clinical trial database evaluation, the AERS data base was searched on March 2, 2004, for adverse events associated with the use of tolterodine in pediatric patients ages 0-16 years of age. Twenty-nine unduplicated cases (25 treated with Detrol tablets and 4 treated with Detrol LA capsules) aged 11 months to 16 years of age were found. Although the majority of the cases were not serious, five of these patients required hospitalization. One of these cases (breathing difficulty, laryngitis, and coughing) appeared to be plausibly related to tolterodine due to onset of symptoms five days after starting Detrol and a positive dechallenge. A second hospitalization occurred in a 12 year old child who experienced "heart block," dizziness, chest pain and fatigue while taking tolterodine and several immunosuppressive drugs. A third case involved a five-year-old hospitalized with a seizure while taking Detrol. The remaining two hospitalized cases either were associated with a plausible etiology unrelated to tolterodine or experienced a negative dechallenge.

Ten cases, in children aged five to 16 years, were events associated with CNS stimulation (aggression, hyperactivity, irritability, and insomnia). Two of these patients (both males, aged 8 and 16 years) had a history of attention deficit hyperactivity disorder (ADHD). In six patients (all males, aged 8 to 16 years) the CNS events ceased when tolterodine was discontinued. No

dechallenge information was reported for the 4 remaining cases (3 females, 1 unspecified, aged 5 to 15 years). One 8 year old male patient with a history of ADHD experienced hyperactivity that abated upon tolterodine discontinuation and reappeared after tolterodine was reintroduced.

6.3 Summary of Safety

Upon review of the available pediatric safety data, three signals of concern were noted:

- Increased frequency of UTI in subjects exposed to tolterodine
- Increased frequency of psychiatric/behavioral disorders, including aggressive behavior, seen in children treated with tolterodine. Such reports were noted both in the clinical trial data and in spontaneous case reports in the AERS database. Although data from the AERS database do not provide clear information about incidence or prevalence of adverse effects because of lack of a denominator, it is notable that about one-third of all reported pediatric cases were related to behavioral disorders, a number of which showed a positive dechallenge response. These behavioral problems may represent a CNS stimulatory reaction in children exposed to tolterodine.
- Rare reports of initiation or exacerbation of seizures in children on tolterodine, both in the clinical trial data and in the AERS database. While the treatment-relatedness of these reactions is difficult to assess, it is plausible that a CNS stimulatory effect might lower the seizure threshold and cause worsening of an existing seizure disorder.

7.0 Clinical Pharmacology:

The clinical pharmacologist reviewed two PK studies (044 and 018), two bioavailability studies (004 and 005), three PK/PD studies (001, 002, and 003), and two phase 3 efficacy studies (020 and 008). Population PK analyses conducted on data pooled from Studies 018, 044, 020, and 008 were also reviewed.

Study 004 compared the relative bioavailability of the beads from opened tolterodine extended release capsules to the intact capsules in 30 healthy adult volunteers. Although AUC for the two methods of dosing was found to be bioequivalent (for tolterodine, the active metabolite, DD 01, and the active moiety [the sum of unbound tolterodine and DD 01]), C_{max} of the three moieties was not. The beads had a 21% higher C_{max} for tolterodine than the intact capsule.

Study 005 evaluated the relative bioavailability of tolterodine immediate release and two formulations of tolterodine oral syrup in 24 healthy adult volunteers. Bioequivalence was demonstrated for DD 01 and the active moiety for both AUC and C_{max}, but was not demonstrated for tolterodine itself. The "prototype" formulation used in Studies 001 and 002 had a 19% higher tolterodine AUC and a 16% higher C_{max} than the tablet.

Review of the three PK/PD studies in children with neurogenic lower urinary tract dysfunction found no evidence of a dose-response relationship. Plotting the AUC and Cmax of both tolterodine and the active moiety against the change from baseline in volume to first detrusor contraction displayed no correlation in Trials 001, 002, or 003. An example of individual dose response data from Trial 001 is shown in Figure 1.

Figure 1. Change from Baseline in Volume to First Detrusor Contraction: Data from Study 001

(b)(4)

Study 018, which evaluated extended release tolterodine, demonstrated that, in children aged 11 to 15 years, Detrol LA produced equivalent exposure at the same dose as adults. Study 044 in 5 to 10 year old children showed that exposure in children receiving immediate release (IR) tolterodine 1 mg bid was similar to that in adults taking twice that dose, 2 mg bid, of the same formulation. Previous studies in adults have demonstrated that equivalent daily doses of tolterodine immediate release and extended release provide similar exposure. However, studies presented in this NDA submission did not show a similar relation in children between the IR and LA doses. Based on these findings, the phase 3 trials were constructed to treat 5-10 year old children with 2 mg daily of tolterodine extended release, that is half the usual adult dose.

Population PK/PD analysis using pooled data from Trials 008 and 020 indicated that the 2 mg/day dose of extended release tolterodine provided drug exposure below (31% lower) that seen in adults with 4 mg/day. A Classification and Regression Tree procedure was used to identify breakpoints in the AUC of the active moiety associated with response on the clinical outcome measure, number of incontinence episodes. Using this procedure, threshold exposure levels were identified of 12.6 nM*h in Study 020 and 14.4 nM*h in Study 008. Multivariate regression analysis showed that the two covariates predictive of clinical response were baseline frequency of incontinence and whether or not the threshold exposure had been achieved.

8.0 Conclusion:

Because efficacy was not demonstrated in either children with neurologic disease (Trials 001, 002, and 003) or neurologically normal children (Trials 008 and 020), an indication for pediatric use cannot be justified in the label. Adverse events (increased risk of urinary tract infection and behavioral disorders) which should be incorporated into the Detrol LA label were identified in the two placebo-controlled studies.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames

4/9/04 12:39:31 PM