

**Public Clinical Assessment Report
Paediatric data**

**Detrusitol/Detrusitol SR/Detsel/Protol SR
(tolterodine tartrate)**

Marketing Authorisation Holder: Pfizer AB

Date of this report:	13.09.2006
Currently approved indication	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.
Pharmaceutical form affected by this variation	Film-coated tablet and prolonged-release capsule, hard
Strength(s) affected by this procedure	Detrusitol and Detsel: 1 mg and 2 mg film-coated tablet Detrusitol SR and Protol SR: 2 mg and 4 mg prolonged-release capsule, hard

I. RECOMMENDATION

This is a review of the documentation submitted in the Paediatric data assessment procedure. The applicant has not submitted a special expert report and does not wish for any inclusion of information in the SPC. The FDA has included the following statement in their labelling. This is presently stated under precautions

“Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release (DETROL LA) capsules. A total of 710 pediatric patients (486 on DETROL LA and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behaviour and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.”

Based on the review, the paediatric data should lead to the inclusion of the following SPC text:

4.2 (Posology and method of administration):

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children (See section 5.1). Therefore, Detrusitol/Detrusitol SR is not recommended for children.

4.8 (Undesirable effects):

In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine 6.8 %; placebo 3.6 %, diarrhoea: tolterodine 3.3 %; placebo 0.9 % abnormal behaviour: tolterodine 1.6 %; placebo 0.4 %). (See section 5.1)

5.1 (Pharmacodynamic Properties):

Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed in either study with regard to (change from baseline in total number of incontinence episodes/week). (See section 4.8)

5.2 (Pharmacokinetic Properties):

Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (See sections 4.2 and 5.1).

I.1 Scope of the variation

This is not a formal variation. The applicant does not wish for any inclusion of information in the SPC.

II. SCIENTIFIC DISCUSSION

II.3 Clinical aspects

III.3.1 Clinical pharmacology

Pharmacokinetic characteristics of tolterodine

After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite. The absolute bioavailability of tolterodine is 17 % in extensive metabolisers, the majority of the patients, and 65% in poor metabolisers (devoid of CYP2D6). Tolterodine and the 5-hydroxymethyl metabolite bind primarily to orosomucoid. The unbound fractions are 3.7% and 36%, respectively. Tolterodine is extensively metabolised by the liver following oral dosing. The primary metabolic route is mediated by the polymorphic enzyme CYP2D6 and leads to the formation of the 5-hydroxymethyl metabolite. The 5-hydroxymethyl metabolite is pharmacologically active and equipotent with tolterodine. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The exposure of “active moiety” has generally been used in the pharmacokinetic studies as it is stated to be the exposure correlated to clinical effect. The exposure of active moiety is calculated based on the protein binding and exposure of tolterodine and the 5-hydroxymethyl metabolite.

Critical evaluation

Comparison of clinical trial formulations with marketed formulations

Oral solution: The relative bioavailability of tolterodine, its active metabolite and the “active moiety” was investigated after administration of tolterodine 4 mg single-dose as tablets and as two oral solutions in healthy young adult subjects was investigated in study 583E-URO-0581-005. After administration of the commercial and the prototype liquid formulation, the criteria for equivalence were fulfilled for the active moiety and active metabolite, DD 01 in extensive metabolizers. Bioequivalence was not shown for the parent drug, tolterodine, for which higher C_{max} and AUC were observed for both solutions. The included subjects were extensive metabolisers.

Table 1 The relative bioavailability, AUC_{0-∞} ratio, C_{max} ratio and 90% confidence intervals.

	AUC _{0-∞}		C _{max}	
	Liquid Commercial vs IR Tablet, N=24	Liquid Prototype vs IR Tablet, N=24	Liquid Commercial vs IR Tablet, N=24	Liquid Prototype vs IR Tablet, N=24
Active moiety	1.047 (1.003, 1.094)	1.017 (0.974, 1.062)	1.075 (0.982, 1.177)	0.961 (0.878, 1.052)
Tolterodine	1.231 (1.081, 1.402)	1.191 (1.046, 1.356)	1.306 (1.097, 1.553)	1.163 (0.978, 1.384)
DD01	1.068 (1.002, 1.137)	1.043 (0.980, 1.111)	1.089 (0.986, 1.204)	0.984 (0.890, 1.087)

Opened prolonged release capsules: The relative bioavailability of the beads from opened capsules sprinkled over applesauce to intact tolterodine 4 mg prolonged release capsules was investigated in healthy extensive metabolisers volunteers after a 4 mg single-dose under fasting conditions (study 583E-URO-0581-004). Bioequivalence was shown with respect to AUC for Tolterodine, active metabolite and active moiety. However, C_{max} was slightly higher for the beads.

Table 2 AUC mean ratios and 90% confidence intervals

Substance		beads vs. intact capsule
Tolterodine	Geometric Mean	1.00
	90% Confidence Interval	(0.91, 1.09)
DD01	Geometric Mean	1.01
	90% Confidence Interval	(0.97, 1.06)
Active moiety	Geometric Mean	1.08
	90% Confidence Interval	(1.03, 1.14)

Table 3 C_{max} mean ratios and 90% confidence intervals

Substance		beads vs. intact capsule
Tolterodine	Geometric Mean	1.21
	90% Confidence Interval	(1.07, 1.37)
DD01	Geometric Mean	1.23
	90% Confidence Interval	(1.12, 1.35)
Active moiety	Geometric Mean	1.31
	90% Confidence Interval	(1.21, 1.43)

Assessors comment

As the formation of the active metabolite is dose-linear, bioequivalence should be based on tolterodine alone. Pooling of parent drug and metabolite data is not allowed. The oral solution is not equivalent to the conventional tablets. The exposure of tolterodine was higher after intake of the oral solution.

Administration of the beads of the prolonged release capsules was equivalent to the closed capsules with respect to tolterodine AUC but gave a higher C_{max}.

Pharmacokinetics in paediatric patients

The applicant has performed several pharmacokinetic studies in patients of different age. In addition, population analyses based on sparse sampling from clinical studies and rich data from pharmacokinetic studies has been performed. Below the specific studies and results are presented. The exposure of active moiety will be focused on as this pooled parameter has been associated to the clinical effect of Detrusitol, takes into account protein binding of the active substances as well as make the inclusion of poor metabolisers possible.

In study **583E-URO-0084-018** the pharmacokinetics of tolterodine 2 and 4 mg q.d. (PR formulation) for 6-10 days in 11 – 15 year-old paediatric patients was studied. Blood sampling was performed for 0-25 hours post-dose on the last treatment day.

Table 4 Pharmacokinetics of tolterodine and metabolites in patients between 11 and 15 years after treatment with 2 and 4 mg q.d. for 6-10 days.

		Treatment		
		2-mg dose		4-mg dose
Variable		Extensive Metabolizer N=7	Poor Metabolizer N=2	Extensive Metabolizer N=20
AUC ₀₋₂₄ (µg·h/L)	Mean (SD)	39.4 (37.5)	210.5 (18.6)	42.8 (34.2)
	Median (min-max)	25.6 (2.5 -108.5)	210.5 (197.3 -223.7)	31.0 (8.7 -123.8)
C _{max} (µg/L)	Mean (SD)	3.22 (2.94)	10.76 (2.74)	3.43 (2.60)
	Median (min-max)	1.91 (0.35 -8.34)	10.76 (8.82 -12.70)	2.58 (0.56 -9.87)
T _{max} (h)	Mean (SD)	3.57 (1.28)	3.51 (0.72)	3.85 (1.57)
	Median (min-max)	3.00 (1.98 -6.00)	3.51 (3.00 -4.02)	3.53 (1.95 -6.97)
t _{1/2} (h)	Mean (SD)	13.6 (4.5)	165.6 (161.4)	16.6 (13.4)
	Median (min-max)	14.2 (5.4 -17.7)	165.6 (51.5 -279.8)	9.9 (5.8 -52.7)
V _{ss} /F (L)	Mean (SD)	1204 (1366)	145 (26)	1492 (1223)
	Median (min-max)	637 (195 -4031)	145 (127 -163)	922 (224 -4304)
Cl/F (L/h)	Mean (SD)	103.6 (185.0)	1.06 (0.92)	81.2 (66.6)
	Median (min-max)	39.5 (7.9 -520.1)	1.06 (0.40 -1.71)	65.3 (10.9 -234.7)
Pharmacokinetic variables for DD 01 in extensive metabolizers.				
		Treatment		
		2-mg dose		4-mg dose
Variable		Extensive Metabolizer N=7	Extensive Metabolizer N=20	
AUC ₀₋₂₄ (µg·h/L)	Mean (SD)	20.6 (9.2)	32.9 (11.6)	
	Median (min-max)	18.5 (7.2 -34.4)	31.0 (18.5 -54.1)	
C _{max} (µg/L)	Mean (SD)	1.33 (0.56)	2.38 (1.01)	
	Median (min-max)	1.26 (0.71 -2.43)	2.38 (1.04 -5.44)	

Tmax (h)	Mean (SD)	4.71 (1.25)		5.00 (2.02)	
	Median (min-max)	4.00 (3.00 -6.00)		5.05 (1.97 -9.00)	
t½ (h)	Mean (SD)	14.8 (3.2)		15.3 (11.5)	
	Median (min-max)	13.6 (11.6 -19.6)		13.0 (6.4 -51.4)	
. Pharmacokinetic variables for the active moiety in all patients					
		Treatment			4-mg dose
		2-mg dose			
Variable		Extensive Metabolizer N=7	Poor Metabolizer N=2	All N=9	Extensive Metabolizer N=20
AUC0-24 (nM·h)	Mean (SD)	17.3 (6.0)	12.3 (0.2)	16.2 (5.6)	29.7 (11.1)
	Median (min-max)	17.4 (7.5 -24.7)	12.3 (12.2 -12.5)	16.2 (7.5 – 27.7)	26.7 (14.4 -52.3)
Cmax (nM)	Mean (SD)	1.23 (0.33)	0.62 (0.09)	1.10 (0.39)	2.17 (0.95)
	Median (min-max)	1.34 (0.75 -1.57)	0.62 (0.56 -0.69)	1.19 (0.56 – 1.57)	2.07 (0.93 -5.25)

The exposure (AUC₀₋₂₄) to the active moiety in this study, 30.5 ±11.0 nM·h, was comparable to the average exposure in adult historical controls (see below) after administration of 4 mg PR capsules, but higher than the average exposure in adults after administration of IR tablets. C_{max} at steady state after treatment with the PR capsule has only been determined in one study in adults.

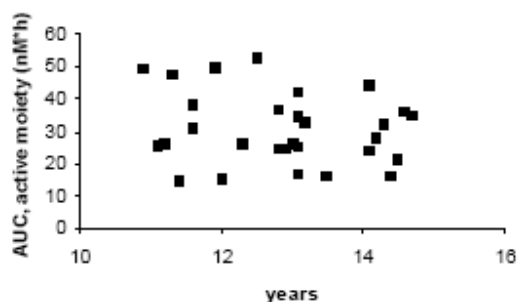
Table 5 AUC and C_{max} of active moiety in 10-15 year-old children and adults normalised to a 4 mg dose

Variable		PR capsule		IR tablet
		Children ₁ *4 mg N=29	Adults ₂ 4mg N=17	Adults ₃ *4 mg N=183
AUC0-24 (nM·h)	Mean (SD)	30.50 (11.00)	30.4 (13.7)	24.7 (8.8)
C _{max} (nM)	Mean (SD)	2.18 (0.89)	2.3 (1.0)	-

There was a negative correlation between weight and AUC (P=0.045), and weight and C_{max} (P=0.021) (Figures 1a and b). There was no clear correlation with age.

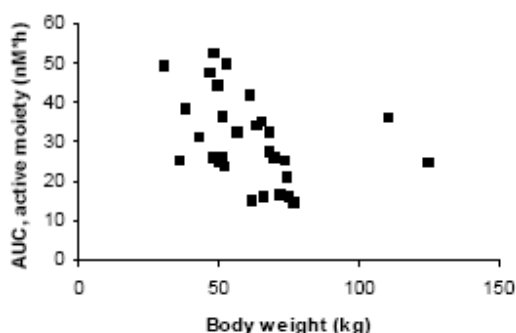
Figure 1 AUC of active moiety vs. age (a) and weight (b). Data normalised to 4 mg q.d.

Figure 9.3.1.1 AUC₀₋₂₄ of active moiety (*4 mg-dose) vs. age, (N=29).



b)

Figure 9.3.1.3 AUC₀₋₂₄ of active moiety (*4-mg dose) vs. body weight, (N=29).



Assessors comment: It is noted that the poor metabolisers had lower active moiety exposure than the extensive metabolisers on the same dose (2 mg). The half-life of tolterodine was extremely long in one PM – 280 hrs, in the other PM, the half-life was 52 hrs. Thus, steady state was not reached and borderline reached for the two PMs. respectively.

In study 583E-URO-0581-003 the pharmacokinetics was studied after treatment with 4 mg/day tolterodine as PR capsules for 4 weeks in patients 11 to 15 years of age with detrusor hyperreflexia. The results are presented below.

Table 6. Pharmacokinetic Parameters for the Active Moiety after the 4 mg Once Daily Dose (N=10)

Parameter	Statistic Active Moiety N=10	
	Mean (SD)	Median (min, max)
AUC ₀₋₂₄ (nM*hr)	27.3 (10.5)	25.5 (11.5, 43.4)
C _{max} (nM)	2.10 (0.93)	1.89 (1.03, 3.86)
C _{min} (nM)	0.619 (0.272)	0.599 (0.237, 1.233)

Table 8. Pharmacokinetic Parameters for Tolterodine and DD 01 After 4 mg/day Regimen

Parameter	Statistic	Tolterodine		DD 01
		Extensive Metabolizer N=7	Poor Metabolizer N=3	Extensive Metabolizer N=7
AUC ₀₋₂₄ (µg*hr/L)	Mean (SD)	48.3 (41.1)	331.5 (19.8)	30.5 (6.0)
	Median (min, max)	31.2 (8.0, 129.8)	326.1 (315.0, 353.5)	32.7 (20.0, 36.9)
C _{max} (µg/L)	Mean (SD)	4.63 (3.01)	18.77 (1.42)	2.58 (0.72)
	Median (min, max)	3.93 (0.69, 8.77)	18.00 (17.90, 20.40)	2.43 (1.80, 3.89)
t _{max} (hr)	Mean (SD)	3.29 (0.49)	3.30 (0.61)	3.86 (1.07)
	Median (min, max)	3.00 (3.00, 4.00)	3.00 (2.90, 4.00)	4.00 (3.00, 6.00)
C _{min} (µg/L)	Mean (SD)	0.980 (0.938)	9.723 (1.973)	0.646 (0.320)
	Median (min, max)	0.677 (0.204, 2.980)	8.650 (8.520, 12.000)	0.572 (0.363, 1.190)
t _{1/2,z} (hr)	Mean (SD)	8.86 (4.00)	28.89 (10.72)	11.38 (8.03)
	Median (min, max)	8.53 (3.67, 13.44)	25.74 (20.10, 40.84)	9.46 (3.40, 28.04)
CL/F (L/hr/kg)	Mean (SD)	2.20 (2.03)	0.14 (0.01)	NC

Median (min, max) 1.85 (0.40, 6.62) 0.14 (0.13, 0.15)

Fig 2a AUC₀₋₁₂ of active moiety versus age

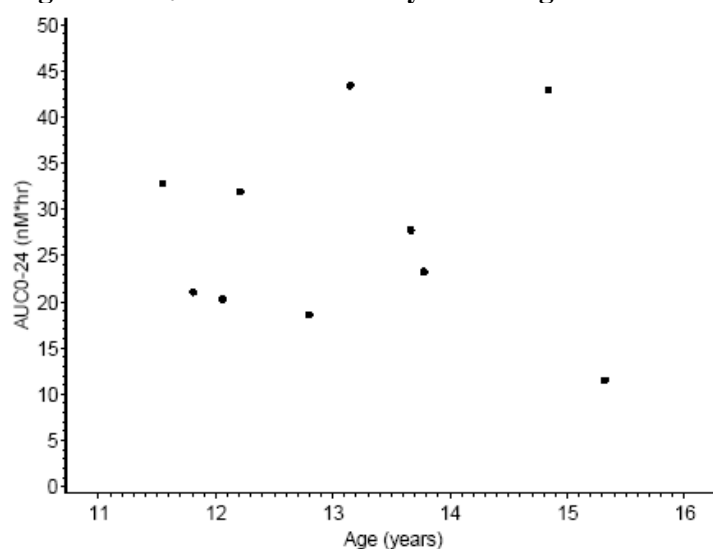
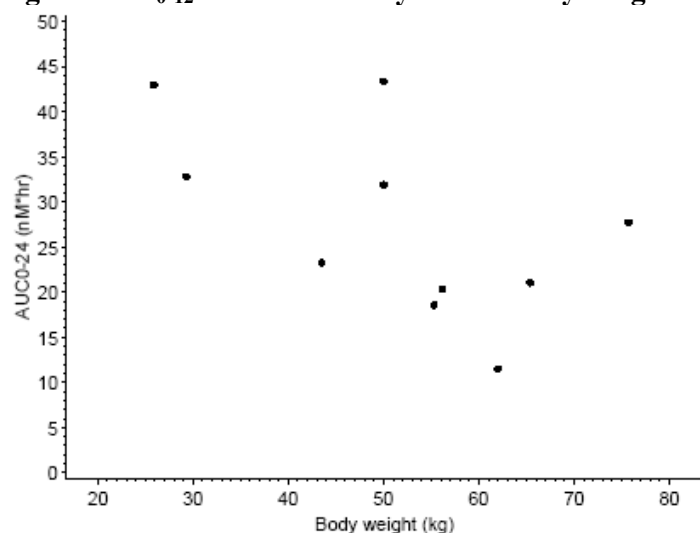


Fig 2b AUC₀₋₁₂ of active moiety versus body weight



Assessors comment on the pharmacokinetic documentation in the age group 10-15 years:

The pharmacokinetics appears similar in patients in this age group and in adults. This is as expected. There seems to be a inverted relationship between body weight and exposure, Patients of lower weight have higher exposure of active moiety.

The pharmacokinetics of tolterodine (Ia), DD 01 (IIa), dealkylated tolterodine(Ib), dealkylated hydroxylated tolterodine (IIb), tolterodine acid (IVa) and dealkylated olterodine acid (IVb) was investigated after administration of 0.5, 1, 2 mg b.i.d. as conventional tablets for 14 days in patients between 5 and 10 years of age in study **PNU-583-URO-0087 (Report CTN 97-OATA-044)**. This study was intended to include also a 3 mg b.i.d. arm but as highest “allowed” AUC was reached already during 1 mg b.i.d. the study was stopped after 2 mg b.i.d. Blood sampling was performed 0-3 hours post-dose on day 1 and at 0-8 hours post-dose on day 14. The subjects received a light breakfast just before drug administration on the sampling days.

A dose of 2 mg b.i.d. resulted in an unbound AUC_{0-12hrs} of active moiety of 32±16 ug*h/mL. Treatment with 1 mg b.i.d. gave approximately half of the exposure. The degree of accumulation was estimated to 1.1-1.3 for tolterodine, DD01 and the other metabolites. Unfortunately, there was no presentation of dose normalised exposure vs weight or age.

Tables 9 a and b Pharmacokinetics of tolterodine, DD01 and active moiety in paediatric patients between 5 and 10 years.

C_{max} and AUC (mean ± SD) of active moiety

EM and PM patients day 14	0.5 mg bid	1 mg bid	2 mg bid
C _{max} (nM)	1.8 ± 0.8	3.9 ± 1.4	7.6 ± 3.0
AUC (nM ·h)	7.2 ± 2.4	13.9 ± 4.9	30.9 ± 9.7

n =10 in each group

C_{max}, AUC_{0-12h}, T_{max} and t_{1/2} (mean ± SD) of tolterodine and DD.

EM patients day 14		0.5 mg bid	1 mg bid	2 mg bid
C _{max} (µg/L)	Tolterodine	3.4 ± 3.0 n=9 ^a	4.9 ± 2.9 n=10	11.5 ± 6.5 n=9 ^b
	DD 01	2.0 ± 0.9 n=9	4.6 ± 1.7 n=10	8.5 ± 4.0 n=9
AUC (µg·h/L)	Tolterodine	11.2 ± 13.5 n=9 ^c	14.8 ± 10.2 n=10	31.7 ± 16.3 n=9 ^d
	DD 01	7.6 ± 2.5 n=9	17.4 ± 8.3 n=10	34.1 ± 12.0 n=9
T _{max} (h)	Tolterodine	1.4 ± 0.9 n=9 ^e	1.2 ± 0.6 n=10	1.3 ± 0.7 n=9 ^f
	DD 01	1.5 ± 0.8 n=9	1.6 ± 0.6 n=10	1.6 ± 0.6 n=9
t _{1/2} (h)	Tolterodine	1.8 ± 1.1 n=9 ^g	1.4 ± 0.4 n=10	2.0 ± 0.8 n=9 ^h
	DD 01	2.6 ± 1.3 n=9	2.1 ± 0.3 n=10	2.6 ± 1.0 n=9

PM patients: ^aNo. 9 C_{max} = 6.8; ^bNo. 29 C_{max} = 41.6; ^cNo. 9 AUC = 61; ^dNo. 29 AUC = 211; ^eNo. 9 T_{max} = 4.1; ^fNo. 29 T_{max} = 1; ^gNo. 9 t_{1/2} = 11; ^hNo. 29 t_{1/2} = 3.2

Table 10 C_{max} (mg/L) (mean ±SD) of tolterodine and its metabolites after the doses 0.5, 1 and 2 mg bid, day 14, EM patients.

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	3.4 ±3.0	4.9 ±2.9	11.5 ±6.5
DD 01	2.0 ±0.9	4.6 ±1.7	8.5 ±4.0
Dealkylated hydroxylated tolterodine	0.3 ±0.1	0.7 ±0.3	1.8 ±0.9
Tolterodine acid	3.6 ±1.7	7.5 ±2.9	13.0 ±4.9
Dealkylated tolterodine acid	1.9 ±0.8	3.3 ±0.8	6.6 ±2.3

PM patients: ^aNo. 9 C_{max} = 6.8; ^bNo. 29 C_{max} = 41.6; ^cNo. 29 C_{max} = 0.3

Table 11 AUC_{0-12h}(mg×h /L) (mean ±SD) of tolterodine and its metabolites after the doses 0.5, 1 and 2 mg bid, day 14, EM patients.

	0.5 mg bid	1 mg bid	2 mg bid
Tolterodine	11.2 ±13.5	14.8 ±10.2	31.7 ±16.3
DD 01	7.6 ±2.5	17.4 ±8.3	34.1 ±12.0
Dealkylated hydroxylated tolterodine	‡	3.1 ±0.6	8.7 ±3.5
Tolterodine acid	20.7 ±4.9	39.4 ±8.9	77.1 ±25.3
Dealkylated tolterodine acid	12.0 ±4.2	21.0 ±3.1	48.2 ±12.5

‡ 2.6 and 2.8 mgxh /L

PM patients: aNo. 9 AUC = 61; bNo. 29 AUC = 211;

Assessor's comments: An AUC of active moiety of ca. 30 nM*h has been observed after 4 mg q.d in adults (Table 5). This half the AUC_{0-24 hrs} observed in this study after 2 mg b.i.d. It seems from this data that 1 mg b.i.d. would be the dose giving similar exposure as observed in adults.

In study **583E-URO-0581-002** tolterodine –L-tartrate was administered as oral solution 1 mg/5 mL to 5 to 10 year-old children with detrusor hyperreflexia for 12 weeks (4 weeks at each dose-level). The doses used were 0.030, 0.060, and 0.120 mg/kg/day (to be given in 2 divided doses as conventional tablets). Pharmacokinetic data was collected after treatment with the highest dose for 4 weeks. Fifteen patients were enrolled and completed the study. The median age of the patients was 8 years; 8 patients were 8 to 11 years old and 7 patients were 5 to 7 years old. The actual median dose administered on the PK sampling day was 0.71 mg b.i.d (range 0.48-1.75 mg). The mean unbound AUC_{0-12hrs} of active moiety was 7.4±4.7 nM*h. Slightly lower exposures were found in this study than the before mentioned study in patients aged between 5 and 10 years when correcting for the difference in dose (Table 12). No relation was found between unbound AUC of active moiety and age or bodyweight (Fig 3).

Table 12 Pharmacokinetics in children 5-10 years of age after 0.03 mg/kg b.i.d. (average 0.71 mg b.i.d.)

	Tolterodine		DD 01	Active Moiety
	EM (n=12)	PM (n=1)	EM (n=12)	EM and PM (n=13)
AUC ₀₋₁₂	10.4 (9.3) µg*hr/L	50.5 µg*hr/L	9.1 (7.4) µg*hr/L	7.4 (4.7) nM*hr
C _{max}	3.28 (2.18) µg/L	9.88 µg/L	2.18 (1.98) µg/L	1.78 (1.30) nM
t _{max}	1.01 (0.53) hr	0.97 hr	1.14 (0.57) hr	NC
C _{min}	0.17 (0.38) µg/L	1.62 µg/L	0.12 (0.13) µg/L	0.10 (0.11) nM
t _{1/2,z}	2.20 (1.00) hr	3.88 hr	3.01 (1.53) hr	NC

EM=extensive metabolizer; NC=not calculated; PM=poor metabolizer

Fig 3 A: AUC₀₋₁₂ of active moiety versus age

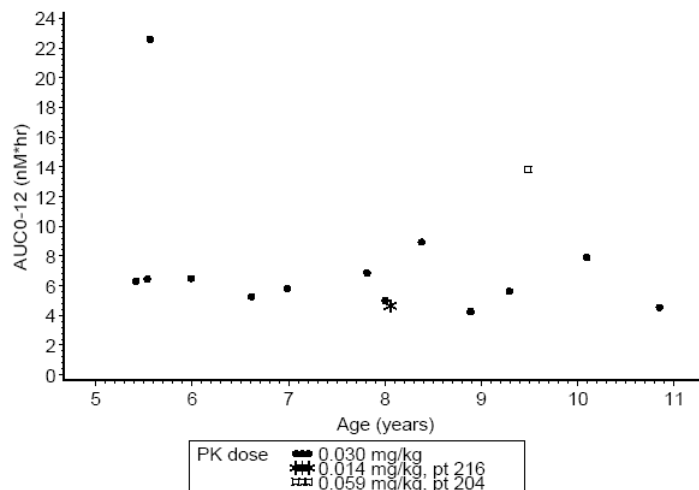
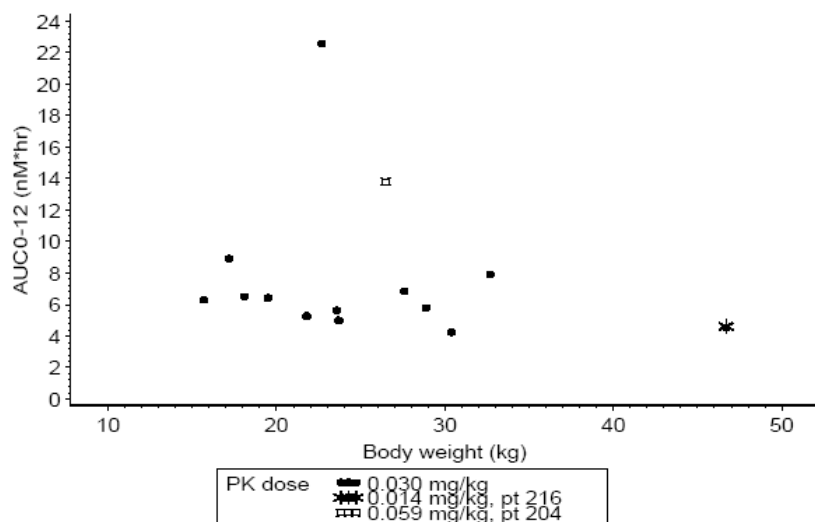


Fig 3 B: AUC₀₋₁₂ of active moiety versus body weight



Assessors comment on the exposure of active moiety in children aged 5-10 years.

The study results are slightly different. In the first study a dose of 1 g b.i.d. gave similar AUC_{0-24h} as 4 mg q.d to adults. In the second study, the AUC_{0-24 hours} after a mean dose of 0.03 mg/kg b.i.d. (0.71 mg b.i.d.) was 15 nM*h. A dose of ca. 0.06 mg/kg b.i.d. (approx. 1.4mg b.i.d.) would give similar exposure to the therapeutic adult exposure. There is one 5-year-old subject with 3 times higher exposure than the mean exposure. The reason for this is unknown.

In study **583E-URO-0581-001** the pharmacokinetics of tolterodine oral solution in paediatric patients aged 1 month to 4 years was investigated. The median age of all patients was 2 years; three patients were under 6 months old, six patients were 6 months to <2 years old, and 10 patients were 2 to 4 years old. Tolterodine-L-tartrate 0.030 mg/kg had been administered b.i.d. for 8 weeks at the day of pharmacokinetic sampling (0-8 hrs post-dose). AUC_{0-12hrs} was extrapolated using the terminal rate constant and C_{8hrs}. A 0.030 mg/kg dose of tolterodine L-tartrate corresponds to 0.0205 mg/kg of tolterodine. The mean tolterodine dose on the PK sampling day was 0.34 mg (median 0.35, range 0.04-0.66 mg).

Table 13 Pharmacokinetic Results: Mean (SD) pharmacokinetic parameters after the 0.030 mg/kg dose (for the 0.060 mg/kg/day dosing regimen) are presented below.

	Tolterodine		DD 01	Active Moiety
	EM (n=15) *	PM (n=1)	EM (n=15)	EM and PM (n=16)
AUC ₀₋₁₂	8.5 (8.0) µg*hr/L	92.4 µg*hr/L	7.9 (3.9) µg*hr/L	5.9 (2.6) nM*hr
C _{max}	2.86 (2.75) µg/L	13.70 µg/L	2.23 (1.12) µg/L	1.66 (0.61) nM
t _{max}	1.02 (0.59) hr	1.88 hr	1.12 (0.53) hr	NC
C _{min}	0.05 (0.10) µg/L	5.51 µg/L	0.07 (0.10) µg/L	0.08 (0.11) nM
t _{1/2,z}	1.52 (0.58) hr	4.54 hr	2.09 (0.55) hr	NC

* For AUC₀₋₁₂ and t_{1/2,z}, n=12.

EM=extensive metabolizer; NC=not calculated; PM=poor metabolizer.

Drug exposure, as measured by the AUC and Cmax of the active moiety (sum of unbound tolterodine and DD 01), in 1-month-old to 4-year-old patients with detrusor hyperreflexia at the dose of 0.030 mg/kg bid as oral solution (0.060 mg/kg/day) was somewhat lower than that observed previously in 5- to 10-year-old children with overactive bladder receiving 0.03 mg/kg b.i.d. as conventional tablets, and approximately one third that reported in adults receiving 2 mg tolterodine IR tablets twice daily . The AUC₀₋₁₂ hours vs. age and weight are presented in figure 4 a and b, respectively.

Fig 4 A: AUC₀₋₁₂ of active moiety versus age

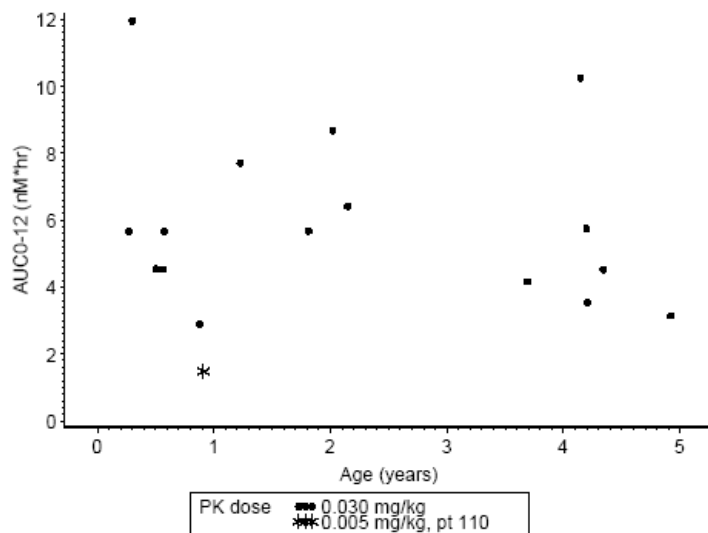
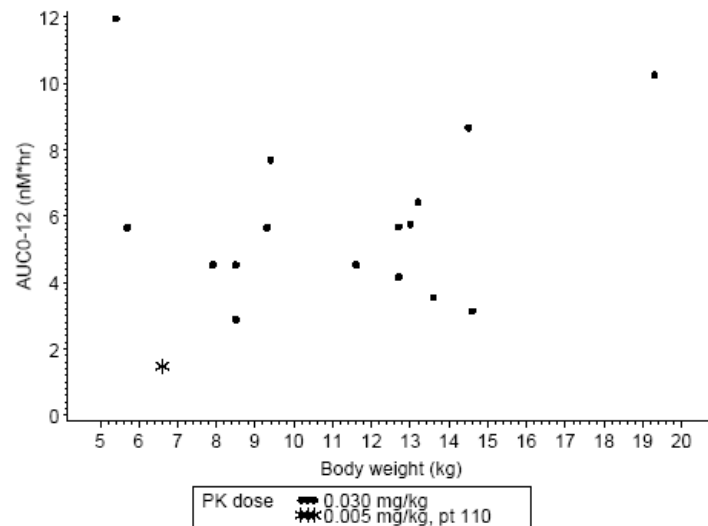


Fig 4 B: AUC₀₋₁₂ of active moiety versus body weight



Assessors comments. There are too few patients in the lower part of the age range for clear conclusions to be made. However, in general the study results indicate that 0.03 mg tolterodine /kg b.i.d. as oral solution to children between 6 months and 5 years gave similar exposure of active moiety as 0.03 b.i.d. as tablets to 5-10 year old children.

Population PK analyses

The applicant has performed 2 population PK analyses. Unfortunately all available data were not included in the analyses. This would have been more informative and would have made more conclusions possible regarding the exposure in the PMs.

The analysis including both rich and sparse data (**DETAPE-0581-XSR2**): rich data from studies 583E-URO-0084-018 and CTN-98-OATA-044 as well as sparse data (and PD measurements) from studies DETAPE-0581-008 (220 patients and 779 plasma concentrations) and 8583E-URO-0084-020 (120 patients and 194 plasma concentrations). The patients received 2 mg q.d. as prolonged release or conventional tablets. The structural model used is shown in figure 5. The final model (including covariates) previously developed from study 018 and study 044 (analysis **DETAPE-0581-XSR1**) was used as the base model to re-evaluate the interindividual variability and magnitude of the covariate effects. The model was evaluated by prediction error, which was -10.4 and 3.3% for tolterodine and the active metabolite, respectively. This final model was used to calculate individual estimates of drug exposure to be used in the pharmacodynamic (PK-PD) and safety analyses. The effect of age as a covariate was not determined. The parameter estimates of the final model are shown in table 15.

Initially, the pharmacodynamic analysis was conducted on the data collected from Study 008 alone. For supportive purposes, additional pharmacodynamic analyses of the combined data from Studies 008 and 020 were performed. Studies 008 and 020 included patients between 5 and 10 years of age. The results of the first analysis (based on study 008) indicated that the factors which were predictive of effectiveness (change from baseline in number of incontinence episodes per week at week 12) were the number of incontinence episodes at baseline and whether or not the patient achieved an active moiety AUC_{0-24} greater than the threshold value of 14.3515 nM*hr. Different dose regimens were simulated. According to the analysis, administration of tolterodine PR 2 mg qd resulted in steady-state AUC_{0-24} values considerably lower than those seen in adults given tolterodine PR 4 mg qd. This was most apparent in patients with a body weight above 25 kg and therefore a 4 mg q.d. dose was simulated in patients weighing over 35 kg (Table 15). Univariable linear regression analyses found AUC_{0-24} of tolterodine, DD 01, and the active moiety (treated as continuous covariates) as statistically significant predictors of effectiveness (p-value = 0.0070, 0.0019, and 0.0010, respectively). However, the adjusted r² values were low (0.0127, 0.0175, and 0.0199, respectively) indicating a poor correlation and that very little of the variability in the change in incontinence episodes was explained.

In the second analysis, based on both study 008 and 020, univariable linear regression analyses found baseline incontinence episodes, gender, and the breakpoints of 21.0705 nM*hr and 12.571 nM*hr as statistically significant predictors of effectiveness (p-value < 0.0001, = 0.0314, = 0.0002, and = 0.0006, respectively). Higher exposure than the high cut-off value was not desirable from a safety point of view. Baseline incontinence episodes explained a large portion of the variability in the change in incontinence episodes from baseline with an adjusted r² of 0.5953. Although both AUC breakpoints were statistically significant, multivariable modeling focused primarily on developing a model using the lower cut-off of 12.571 nM*hr

Figure 5 Structural model

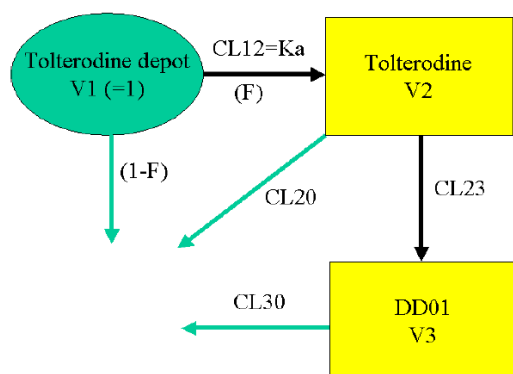


Table 14

Table 4: Parameter Estimates and Standard Errors for the Final Model

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a , absorption rate constant of TTD (1/hr)	0.0473	5.2		
Increase of absorption rate of IR over PR formulation	3.03	7.6		
Coefficient of EM on K_a	0.615	9.6	31.4	26.9
Coefficient of AGE on K_a	-0.353	28.3		
Coefficient of RACC on K_a	-0.289	31.0		
CL20, TTD clearance through intact excretion and other metabolic pathways (L/hr)	17.9	9.3		
Coefficient of WTKG on CL20	0.975	22.6	123	16.1
Coefficient of IR on CL20	-0.627	41.9		
Coefficient of DEC3 on CL20	-0.858	20.5		
Clearance ratio: CL23/CL30	2.10 FIXED	NA	NA	NA
CL23, TTD clearance through conversion to DD 01 (L/hr)	NA	NA		
Coefficient of HTCM on CL23	1.54	43.3	79.0	14.6
Coefficient of AGP on CL23	-1.60	15.9		
Coefficient of RACC on CL23	0.770	10.8		
CL30, DD 01 clearance through intact excretion and other metabolic pathways (L/hr)	67.8	6.1		
Coefficient of IR on CL30	-0.228	46.9	NE	NE
Coefficient of RACC on CL30	0.538	19.3		
Coefficient of HTCM on CL30	2.05	20.0		
Coefficient of AGP on CL30	-1.23	8.3		
V2, Volume of distribution for TTD (L)	46.7	13.1		
Coefficient of IR on V2	-1.16	9.2	216	22.3
Coefficient of AGE on V2	0.758	23.6		
Coefficient of RACC on V2	-1.28	26.6		
Coefficient of AGP on V2	-1.61	17.9		
V3, Volume of distribution for DD 01 (L)	25.5	17.7		
Coefficient of AGP on V3	-1.53	31.0	134	56.4
Coefficient of BSA on V3	1.67	30.2		
Lag time for TTD absorption (hr)	0.715	6.8	35.6	106.3
Residual variability of TTD (%CV)	33.5	19.6	NA	NA
Residual Variability of DD 01 (%CV)	32.6	17.8	NA	NA

Minimum Value of the Objective Function = 230.567
 Note: NA – Not applicable; NE – Not estimated

Table 15 Predicted unbound active moiety $AUC_{0-24hrs}$ using a dose of 4 mg q.d. as PR formulation in patients > 35 kg and 2 mg q.d. in patients ≤35 kg.

Table 20: Summary Statistics for the Predicted Active Moiety AUC₍₀₋₂₄₎ After Administration of the Prescribed Regimen (for Study 008) and for Three Simulated Dosing Regimens, Stratified by Patient Body Weight (kg) (Continued)

		Body Weight (kg)					All
		≤ 20	> 20, ≤ 30	> 30, ≤ 40	> 40, ≤ 50	> 50	
2 or 4 mg daily based on body weight (≤ 35, > 35 kg)	Mean	31.72	25.70	28.51	35.12	28.23	27.68
	SD	7.99	7.62	14.75	9.40	10.36	10.21
	Median	31.62	23.90	25.25	35.08	27.18	26.02
	Min	16.77	6.70	6.43	23.52	6.16	6.16
	Max	65.16	60.81	118.61	61.06	57.48	118.61
	% below 14.4 nM*hr	0.00	3.00	2.98	0.00	7.58	2.86

^a Predicted active moiety AUC₀₋₂₄ for those patients who received 2 mg daily, either as a 2 mg PR capsule QD or 1 mg IR tablet BID.
^b All patients included in the population PK database (n = 385) were used in the simulations. For each regimen, a simulated active moiety AUC₀₋₂₄ was generated individually for an IR tablet and a PR capsule for a total of 770 simulated observations.

The effect of tolterodine was quite modest in studies 008 and 020 and did not differ much from placebo (see figures 11 and 7 below).

Figure 11: Scatterplot of the Final Linear Regression Model for Study 008 Overlaid on the Raw Data

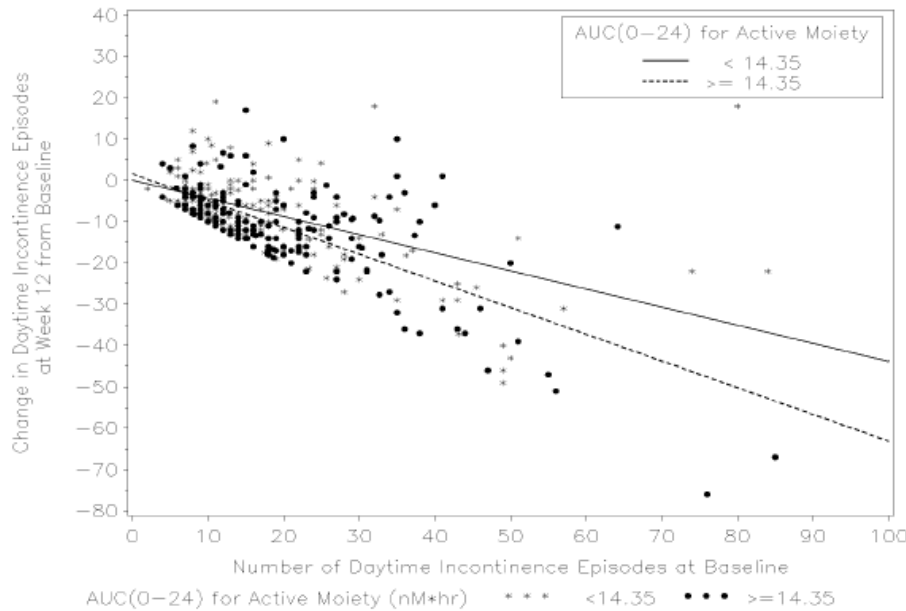
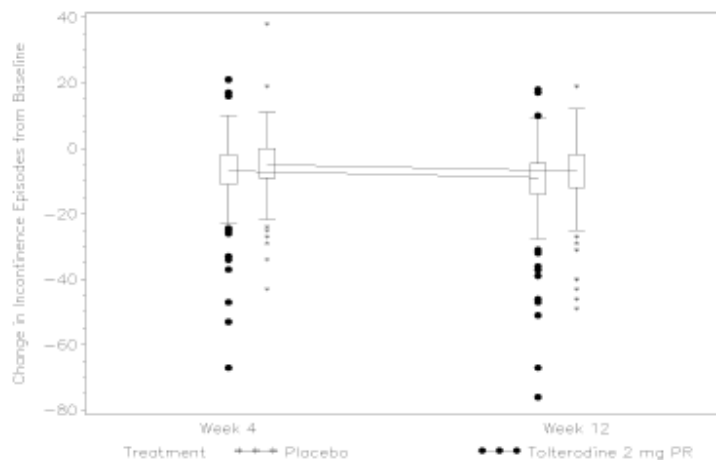


Figure 7: Boxplots of Change in Daytime Incontinence Episodes from Baseline versus Week Stratified by Treatment – Study 008



Assessors comment

Due to the modest effect of tolterodine in the patient population, finding a relationship between exposure and effect is difficult. The analysis found similar results as was found in the conventional studies.

Assessors summary on the pharmacokinetic documentation:

The pharmacokinetics appears similar in patients in children 10-15 years and in adults. This is as expected. In general, there seems to be a inverted relationship between body weight and exposure, Patients of lower weight have higher exposure of active moiety.

Regarding children between 5 and 10 years, the study results are slightly different. In both studies, the exposure of active moiety was higher per mg dose than in adults. In one of the studies, a comparable exposure was reached with the dose 1 mg b.i.d.. In the other study, a dose of 0.06 mg/kg b.i.d. (approx. 1.4mg b.i.d.) would give similar exposure to the therapeutic adult exposure. The population PK analysis suggest that a dose of 2 mg daily to children below the weight of 35 kg and 4 mg daily for children weighing more than 35 kg would give an AUC which is similar to the adult exposure at 4 mg daily. In the clinical studies described below, 2 mg daily was used in the 5-10 year-old population. Approximately 33% of the tolterodine treated patients weighed more than 30kg in study 020 and 27% did so in study 008. It is possible that the lower exposure could have a negative effect on the study results.

*However from the PK-PD analysis, lower target AUC was chosen 12.571 to 21.0705 nM*hr).*

There is little information on the PK in poor metabolisers. However, the enzyme systems involved in the metabolism of tolterodine (CYP2D6 and CYP3A) are likely to equally developed in adults and in these paediatric age groups. Therefore, no further information would be needed.

The pharmacokinetics of active moiety in children between 1 month and 4 years of age was studied at a dose of 0.03 mg/kg b.i.d. At this dose, the mean exposure of active moiety was similar to that observed in 5-10 year-old children treated with the same dose. The data are too sparse in this age group for any assessment of age-differences within the lower age range to be made. However, there were no clear signs of differences in observed exposure within the studied population.

No effect has been substantiated in the clinical studies. However, we are of the opinion that the PK results could be reflected in this text inserted in section 5.2 of the SPC.

“The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults.”

III.3.2 Clinical efficacy

Main studies

The documentation of the clinical efficacy and safety of detrusitol in a paediatric population comprises two multicentre, randomized, double-blind, placebo-controlled studies over 12 weeks, studies 020 and 008. Those studies were followed by an open extension over 12 months, study 021, mainly to evaluate safety. In addition, some smaller open studies were done (table 1).

**Table 1. Overview of Completed and Ongoing Clinical Studies in Children
– Patients Evaluable for Efficacy**

Placebo-controlled	Open label	Treatment Group	Number of Patients/ Dose Group	Total Numbers of Patients
Total number of patients evaluable for efficacy				819
Placebo-controlled therapeutic studies in patients with detrusor overactivity				711
583E-URO-0084-020		Tolterodine PR 2 mg QD	235	342
		Placebo	107	
DETAPE-0581-008		Tolterodine PR 2 mg QD	252 ¹	369
		Placebo	117	
Non-comparative therapeutic studies				298
583E-URO-0084-021		Tolterodine PR 2 mg QD	271 (from 020)	298
		Tolterodine PR 2 mg QD	7 (from 018)	
		Tolterodine PR 4 mg QD	20 (from 018)	
	583E-URO-0581-007*			
	DETAPE-0581-009*			
	583E-URO-0581-006*			
Clinical pharmacology studies				63
CTN-97-OATA-044		Tolterodine IR 0.5 mg BID	11	32
		Tolterodine IR 1.0 mg BID	10	
		Tolterodine IR 2.0 mg BID	11	
583E-URO-0084-018		Tolterodine PR 2 mg QD	10	31
		Tolterodine PR 4 mg QD	21	
Studies in patients with detrusor overactivity of neurogenic origin				45
583E-URO-0581-001		Tolterodine oral solution		19
		1 mg/5 mL BID		
		0.030 mg/kg/day		
		0.060 mg/kg/day		
583E-URO-0581-002		Tolterodine oral solution		15
		1 mg/5 mL BID		
		0.030 mg/kg/day		
		0.060 mg/kg/day		
583E-URO-0581-003		Tolterodine PR QD		11
		2 mg/day		
		4 mg/day		
		6 mg/day		

* Ongoing.

¹ One patient randomized but did not receive treatment

Abbreviations: BID = twice daily, IR = immediate release, PR = prolonged release, QD = once daily.

Summary of study 020

Study 020 was designed to provide efficacy and safety data and to extend the indication for tolterodine PR to include children 5 to 10 years of age. Efficacy was measured by 7-day micturition diary recordings during run-in and during the last week of treatment (week 12). Primary efficacy endpoint was change

from baseline in total number of incontinence episodes/week (during waking hours) after 12 weeks of treatment as obtained by micturition diary.

The entry criterion was at least 1 incontinence episode per day in at least 5 out of 7 days in children with baseline frequency of more than 2 micturitions per 24 hours. The minimum age for entry in the study was 5 years and the upper age limit was 10 years. The dose of the PR formulation selected for this study was one-half of the recommended adult dose of tolterodine PR; that is, a fixed dose of 2 mg to be taken once daily.

Ninety (84.1%) of the 107 placebo subjects and 212 (90.2%) of the 235 tolterodine PR subjects completed this 12-week study. At baseline, the number of incontinence episodes per week was similar in the tolterodine and placebo groups, 14.2 (± 9.3) and 13.8 (± 8.0), respectively. The treatment effect of tolterodine PR in the ITT population was a reduction of approximately 1.54 (± 0.84 SEM) incontinence episodes per week (95% confidence interval = -3.19 to 0.12, $p = 0.0689$) compared to placebo. Thus, treatment difference between tolterodine PR and placebo did not reach statistical significance.

Volume voided per micturition was a secondary efficacy variable. At baseline, the mean volume voided in the tolterodine and placebo groups was similar, 98.7 (± 48.0) and 95.3 (± 43.9) mL, respectively. After 12 weeks of double-blind treatment, the change in mean volume voided was 13.7 (± 32.9) in the tolterodine group versus 5.8 (± 27.8) mL in the placebo group. Thus, the treatment effect of tolterodine PR in the overall study group was an increase of approximately 7.9 ml (± 3.7 SEM) (95% confidence interval = 0.5 to 15.3, $p = 0.0373$).

In the subgroup of patients with at least six micturitions per 24 hours at baseline, the mean change from baseline in the number of incontinence episodes/week for the tolterodine group was 6.5 (± 9.0) and the mean change from baseline in the placebo group was 2.8 (± 6.4). The treatment effect in this subgroup represented a statistically significant reduction of 3.73 incontinence episodes per week ($p = 0.0062$) relative to placebo.

Assessor's comment

The etiological background for the incontinence in the children selected for the study is not clear from the reports. The study results do not show any convincing efficacy with regard to frequency of incontinence, which was the primary endpoint and reason for treatment. The finding that voiding volume increased slightly in the tolterodine group is probably in accordance with its anticholinergic activity and not unexpected. The clinical significance of the finding is, however, doubtful.

Summary of study 008

Study 008 was performed subsequent study to 020. The data from study 020 suggested that the appropriate paediatric patient population for pharmacological interventions consists of those presenting with symptoms of urinary incontinence and ≥ 6 micturitions/24h at baseline. Study 008 was a randomized, double-blind, placebo-controlled, and multicenter, designed to study the efficacy and safety/tolerability of tolterodine PR given qd for 12 weeks to children 5 to 10 years of age with symptoms of urinary urge incontinence suggestive of detrusor instability.

Three critical features distinguished its design from that of study 020:

- In study 008, the inclusion criteria allowed enrolment of only those children with a mean of at least 6 micturitions per 24 hours
- The micturition diary was designed specifically for use in children and was supported with engaging training materials meant to appeal to children.
- In study 008, each patient completed three micturition diaries, one at baseline, one at week 4, and one at week 12.

Efficacy was measured by the 7-day micturition diary recordings. Change from baseline in total number of incontinence episodes/week (during waking hours) after 12 weeks of treatment was the primary efficacy endpoint.

The ITT population comprised 252 patients randomized to tolterodine PR 2 mg qd and 117 patients randomized to placebo. At baseline, the number of incontinence episodes per week in the tolterodine and placebo groups was similar, 19.39 (\pm 13.31) and 18.82 (14.07), respectively. After 12 weeks of therapy, the tolterodine PR group showed a mean reduction from baseline of 10.02 (\pm 12.15) daytime incontinence episodes per week, and the placebo group showed a reduction of 8.79 (\pm 11.13) episodes per week. Thus, the treatment effect of tolterodine PR was a reduction of approximately 0.88 incontinence episodes per week (95% CI = -2.94, 1.18, p = 0.403) compared to placebo.

At baseline, the mean volume voided per micturition in the tolterodine and placebo groups was similar, 85.29 (\pm 38.78) and 84.73 (\pm 36.57) mL, respectively. After 12 weeks of double-blind treatment, the change in mean volume voided per micturition was 18.68 (\pm 40.13) in the tolterodine group versus 9.59 (\pm 27.40) mL in the patients receiving placebo. The treatment effect of tolterodine PR in the overall study group was an increase of approximately 9.16 mL (\pm 4.04 SEM) (95% confidence interval = 1.22 to 17.11 mL, p = 0.024) compared to placebo.

Assessor's comment

Similar results as in study 020 were obtained in study 008, although the study was designed to obtain a more appropriate study group and outcome data. The study was unable to demonstrate any clinically relevant or meaningful effect among paediatric patients with urge urinary incontinence suggestive of detrusor instability.

Summary of long-term open-label study 021

Study 021 was a multicentre, open-label extension study whose primary objective was to evaluate the safety and tolerability of tolterodine PR capsules during 12 months of treatment in children 5 – 15 years old. A total of 298 patients participated. Of those, 271 were recruited as an extension from study 020 and all patients enrolled from study 020 received tolterodine PR 2 mg QD. Moreover, 27 patients with urinary urgency and a frequency and/or urge incontinence with at least one incontinence episode per week, as verified by the micturition diary, were recruited from study 018, which was a small open pharmacokinetic study. Of those, 10 patients received tolterodine 2 mg q.d. and 21 patients received tolterodine 4 mg q.d. Those 31 patients were aged 11 – 15 years. Long-term safety is provided by the data recorded for the 271 patients from study 020, and safety results from those patients are presented in this summary.

Efficacy was measured by change in micturition chart variables from baseline, as assessed in preceding studies, 020 and 018, to months 6 and 12. Visual Analog Scale for Children (VASc) to rate well-being and parent/patient overall assessment of treatment benefit were also included as efficacy assessments. In the population from study 020 (N = 271), there was a decrease from baseline to month 6 in the incidence of incontinence episodes/week (-8.6 ± 8.7), with maintenance of this value at month 12 (-9.1 ± 9.6).

Summary of neurogenic studies 001, 002, and 003

Three studies, 001, 002, and 003, were conducted to determine a tolterodine dose-related pharmacodynamic effect and tolterodine/DD 01 (active moiety) concentration-pharmacodynamic relationship but also provided some efficacy/safety data. These studies were uniform in size (each enrolled ~15 patients). The infants/toddlers in study 001 were 3 months to 4 years of age (mean age: 2.4 years), the children in study 002 were 5 to 10 years of age (mean age: 7.8 years), while the adolescents in study 003 were 11 to 15 years of age (mean age: 13.3 years). All patients had either a congenital neural tube defect or an acquired neurologic condition leading to detrusor overactivity (hyperreflexia).

Each study had a 12-week tolterodine treatment period, consisting of 4 weeks at each of three progressively increasing doses (dose periods 1, 2 and 3: 0.030, 0.060, and 0.120 mg/kg/day of tolterodine oral solution in studies 001, and 002; 2, 4, and 6 mg/day of tolterodine PR for study 003). Patients

continued to a higher dose every 4 weeks after the safety of the preceding dose was assessed as acceptable by the investigator.

Efficacy assessments for studies 001, 002, and 003 included urodynamic variables (volume at first detrusor contraction, functional bladder capacity, intravesical volume, and bladder compliance) as well as micturition diary variables (mean number of incontinence episodes per 24 hours, mean volume per catheterization/micturition, and mean number of catheterizations/micturitions per 24 hours).

In studies 001 and 002, improvements from baseline appeared dose related for both functional bladder capacity and volume to first detrusor contraction and the micturition variables mean number of incontinence episodes per 24 hours and mean volume per catheterization/micturition. Since these patients were managed with a regular schedule of bladder catheterization, the mean number of catheterizations/micturitions per 24 hours did not change with treatment. A dose relationship for the same PD and micturition variables was not observed in study 003.

Assessor's efficacy conclusions

- *The placebo controlled studies could not convincingly demonstrate a clinically meaningful effect of tolterodine for the treatment of symptoms of urge incontinence/overactive bladder syndrome in children 5 to 10 years old. Although not apparent from the study results, it is reasonable to assume that children with symptoms of urge incontinence represent a heterogenous group which, as a group, is not responsive to tolterodine at given doses. The effects of tolterodine reported in studies 020 and 008 on bladder storage capacity, indicating statistically significant increases in mean volume voided per micturition, are not considered clinically meaningful in this population.*
- *The long term follow up study 021 was mainly a safety/tolerability study and did not contribute with meaningful data on efficacy.*
- *The open studies in children with detrusor overactivity of neurogenic origin were not designed to demonstrate clinical efficacy with tolterodine and no conclusions can be drawn.*

III.3.3 Clinical safety

Patient exposure

Clinical safety is based on results from eight studies in 819 children, 595 treated with tolterodine. The program included patients with detrusor overactivity of idiopathic origin: two placebo-controlled studies (studies 020, 008), one long-term extension (study 021), and two small clinical pharmacology studies (018, 044), and, in patients with detrusor overactivity of neurogenic origin, in three dose-escalation studies (studies 001, 002, 003).

The integrated safety dataset from studies 020 and 008 constitute the main safety population and consists of a total of 710 patients, 486 randomized to tolterodine PR and 224 to placebo (table 3). Thus, the safety analyses can estimate the safety profile of tolterodine in patients 5 to 10 years old with detrusor instability. Moreover, data from study 021 (N = 271) provide data for the 12-month safety of tolterodine. The designs of the two open label clinical pharmacology studies, 044 and 018, provide limited safety data, as they were of small size and short duration. The neurogenic dose escalation studies 001, 002, and 003, provide some limited information about the relationship between dose and adverse experiences in patients with detrusor hyperreflexia. The safety findings below come from the analyses of the integrated dataset from studies 020 and 008.

Adverse events

The overall incidence of adverse events was similar in patients treated with tolterodine PR and placebo: 48% vs. 49%, respectively. The most common AEs in patients treated with tolterodine PR were headache (7.2%) and urinary tract infection (UTI; 6.8%); the most common AEs in patients treated with placebo were headache (7.6%) and nasopharyngitis (4.9%).

Adverse events traditionally associated with anticholinergic treatment reported from the tolterodine PR and placebo groups, respectively, were: diarrhea (3.3% vs 0.8%), constipation (2.1% vs 0.8%), and abnormal behaviour (1.6% vs 0.4%). Dry mouth occurred at a higher frequency in placebo-treated patients (1.8%) than in those randomized to tolterodine (0.8%).

There were no occurrences of urinary retention, a theoretical risk with anticholinergic medication. Incidence rates for difficulty in micturition were low and were similar in the tolterodine PR and placebo groups.

Urinary tract infections were more common among tolterodine-treated patients (6.8% vs 3.6%), predominantly girls (12.9% vs 1.2% for tolterodine-treated girls and boys, respectively). The incidence of elevated 'postvoid residual urine volume' (PVR) was higher among patients treated with tolterodine (1.6% vs 0.4%).

The incidence of treatment-related AEs was similar between treatment groups: 16% and 15% in the tolterodine PR and placebo groups, respectively. The most common treatment-related event was headache, 3.5% and 2.7% in the tolterodine PR and placebo groups, respectively.

Discontinuations due to adverse events:

Adverse events led to discontinuation in 3% of patients in each treatment group. The most common AE leading to discontinuation was difficulty in micturition, occurring in five (1.0%) patients in the tolterodine PR group and one (0.4%) in the placebo group.

The pattern of AEs in children with detrusor overactivity of "idiopathic" origin was similar to the pattern in those with detrusor overactivity of neurogenic origin.

Table 3. Most Common (≥1%) Adverse Events: Placebo-controlled Studie

System Organ Class – Preferred Term (MedDRA)	Study 020 + Study 008	
	Tolterodine PR	
	2 mg QD N = 486	Placebo N = 224
	n (%)	n (%)
Gastrointestinal disorders	79 (16.3)	32 (14.3)
– Abdominal pain NOS	22 (4.5)	7 (3.1)
– Vomiting NOS	17 (3.5)	5 (2.2)
– Diarrhea NOS	16 (3.3)	2 (0.9)
– Abdominal pain upper	15 (3.1)	7 (3.1)
– Constipation	10 (2.1)	2 (0.9)
– Nausea	6 (1.2)	5 (2.2)
– Sore throat NOS	6 (1.2)	6 (2.7)
– Dry mouth	4 (0.8)	4 (1.8)
General disorders & administration site conditions	21 (4.3)	14 (6.3)
– Pyrexia	18 (3.7)	10 (4.5)
– Fatigue	3 (0.6)	4 (1.8)
Infections and infestations	60 (12.3)	28 (12.5)
– Urinary tract infection NOS	33 (6.8)	8 (3.6)
– Nasopharyngitis	18 (3.7)	11 (4.9)
– Ear infection NOS	5 (1.0)	1 (0.4)
– Upper respiratory tract infection NOS	5 (1.0)	5 (2.2)
– Influenza	3 (0.6)	5 (2.2)
Musculoskeletal, connective tissue, & bone disorders	2 (0.4)	3 (1.3)
– Arthralgia	2 (0.4)	3 (1.3)
Nervous system disorders	36 (7.4)	18 (8.0)
– Headache NOS	35 (7.2)	17 (7.6)
– Dizziness (except vertigo)	3 (0.6)	3 (1.3)
Psychiatric disorders	8 (1.6)	1 (0.4)
– Abnormal behavior NOS	8 (1.6)	1 (0.4)
Renal and urinary disorders	8 (1.6)	6 (2.7)
– Difficulty in micturition	7 (1.4)	3 (1.3)
– Urinary incontinence aggravated	1 (0.2)	3 (1.3)
Respiratory, thoracic, & mediastinal disorder	24 (4.9)	13 (5.8)
– Cough	12 (2.5)	10 (4.5)
– Rhinitis NOS	8 (1.6)	1 (0.4)
– Epistaxis	5 (1.0)	2 (0.9)
Skin & subcutaneous tissue disorders	8 (1.6)	6 (2.7)
– Dermatitis NOS	7 (1.4)	3 (1.3)
– Eczema NOS	1 (0.2)	3 (1.3)

Serious adverse events and deaths

The incidence of SAEs was 1% in both the tolterodine PR and placebo groups. The only SAE that occurred in more than one patient was pyrexia, in two (0.4%) patients in the tolterodine PR group. The only SAE considered related to treatment was pyelonephritis, in one (0.4%) patient in the placebo group.

Laboratory findings

No laboratory abnormalities which could be considered clinically important were reported. Few clinical laboratory abnormalities were observed and there was no apparent link to treatment with tolterodine. Tolterodine treatment demonstrated no clinically important effect on heart rate or QT/QTc interval.

Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition

Treatment with tolterodine PR over 12 months revealed no new AEs or new patterns of events compared to 12-week treatment.

Dose-adverse event relationship in neurogenic studies:

In the neurogenic studies 001 and 002, the dose-related clinical effect improvements were not matched by dose-related increases in the incidence of AEs, even at the highest dosage (tolterodine oral solution 0.12 mg/kg/day) in each study. In study 003, neither clinical effect improvement nor safety was dose-related.

PSUR findings in paediatric patients:

The PSUR for the reporting period March 2003-March 2004, and a cumulative analysis of all adverse event (AE) reports in patients aged less than eighteen years within the Market Authorization Holder's (MAH) three safety databases for the reporting period up to 31st May 2004 were reviewed. There were a total of 114 non-clinical trial AE reports in the MAH's three safety databases: 76 cases from within the ARGUS database, 19 cases from the ALERT Company legacy database, and 19 case reports from the MEDS Company legacy database. After eleven duplicate reports, identified in the MEDS database, were excluded from further analysis, the 103 non-clinical trial cases were spontaneous in nature, with no literature or solicited sources identified.

The cases containing the serious AEs were described and narratives were provided on the following events: amaurosis fugax, chest pain, dizziness, fatigue, heart block, skin rash, skin exfoliation, dry mouth, urinary retention, post traumatic stress disorder, dyspnea, laryngitis, cough, convulsion, overdose, psychomotor activity, aplasia cutis congenital, drug exposure during pregnancy and drug exposure during pregnancy with outcome of a healthy newborn. Of these 10 cases, three contained insufficient information, which precluded a proper assessment between tolterodine and the reported events.

Assessor's comment on safety

There were no unexpected or alarming findings with regard to safety in the paediatric population studied/exposed. A slightly higher occurrence of gastrointestinal AEs, UTI, postvoid residual urine volume and abnormal behaviour was noted in tolterodine-treated patients compared with placebo.

III. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The placebo controlled studies could not convincingly demonstrate a clinically meaningful effect of tolterodine for the treatment of symptoms of urge incontinence/overactive bladder syndrome in children 5 to 10 years old. Neither were any studies provided that could demonstrate a clinical effect in paediatric patients with neurologic bladder disorders. The small effects of tolterodine reported in studies 020 and 008 on bladder storage capacity are not considered clinically meaningful in this population.

The target patient population for tolterodine treatment are patients suffering from symptoms of overactive bladder syndrome (OAB), a clinical condition with an unknown etiology that becomes increasingly common with age and occurs most often in postmenopausal women. It is uncertain whether a similar condition exists in children and, if so, it could be assumed that possible etiological factors in children differ substantially from those behind OAB in adult and ageing patients. Therefore, it is unlikely that pharmacokinetic results obtained in children can be extrapolated to also reflect a clinical effect in children. In order to theoretically justify further clinical trials with tolterodine in paediatric patients, it is proposed that the clinical condition be carefully described and well defined in children, for example as neurologic bladder disorder, urogenital malformations or other conditions that could be described in detail by use of micturition diaries etc, and that such patient groups are studied separately in large enough controlled studies.

The safety analysis showed a slightly higher rate of gastrointestinal AEs, UTI, post-void residual urinary volume and abnormal behaviour in children treated with tolterodine.

The lack of efficacy in children should be reflected in the SPC.

SPC comments

In section 4.2 Posology and method of administration, the following text is proposed:

Children:

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children. Therefore, Detrusitol/Detrusitol SR is not recommended for children.

In section 5.2 this should be added:

Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults.

IV. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEUR

The rapporteurs do not wish to request supplementary information.

V. RESPONSE BY MS AND RAPPORTEURS COMMENTS

In general, all responding member states endorsed the overall conclusions of the Rapporteur. The Co-rapporteur did not submit an assessment report. There were comments with regard to which information should be provided in the SPC, sections 4.2, 4.8, 5.1 and 5.2.

The following comments were made:

Comments from MS

Overall conclusion on the medicinal product:

The MS agrees in general with the overall conclusions of the Rapporteur, but some of the SPC texts proposed in D70 Assessment Report warrant further discussion.

SPC - points for consideration:

4.2: The recommendation not to use Detrusitol in children is not necessary once the lack of demonstration of efficacy has been clearly stated. In other words, the 2nd proposed sentence “Therefore, Detrusitol/Detrusitol SR is not recommended for children.” may be omitted.

4.8: A short notion of the sensitivity of children to gastrointestinal AEs, urinary tract infections, micturition difficulties and abnormal behaviour should be added to section 4.8.

5.2: This section is suggested to be amended with the PK results “The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults.” The 2nd sentence does not appear to be in line with the data given in D70 AR. According to table 5 AUC of the active moiety in adults normalised to a 4 mg dose is 30.4 nM.h, and later on in table 9a&b it reads that AUC of the active moiety is 30.9 nM.h in children 5-10 years of age treated

with 2 mg bid. Thus, isn't the exposure of the active moiety per mg dose factually the same in all studied age groups ?

Rapporteur's comment: Table 9 refers to AUC_{0-12hrs} while the figure for adults (Table 5) refers to AUC_{0-24 hrs}. Thus, the exposure is about doubled in 5-10 year old children.

Comments from MS:

Following review of the Day 70 AR of Paediatric Data in relation to Detrusitol, I agree with the conclusions of the Rapporteur and endorse the proposed text for inclusion in the SPC. No further comments.

Comments from MS:

In MS DETRUSITOL prolonged-release capsules of tolterodine tartrate, are approved for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

The current text in the MS SmPC states that safety and efficacy in paediatric patients have not been evaluated and therefore is not recommended.

In assessment of Paediatric data of DETRUSITOL the applicant does not wish any inclusion of information in the SPC.

We agree with the overall conclusion made by the Rapporteur and with the information for section 4.2 "use in children"

After analysing the submitted data we suggest further discussion in order to decide or not to include in the SPC information gather by the two paediatric phase 3 randomised, placebo-controlled, double bind, mainly in sections 4.8 and 5.1, taking the example of FDA.

Comments from the MS

In general we endorse the conclusion of the Rapporteur. We would however propose that in addition to the Rapporteur's proposals that:-

-Those adverse effects which have been observed more frequently in children treated with tolterodine than placebo (i.e urinary tract infections, diarrhoea and abnormal behaviour) are incorporated into section 4.8 of the SmPC.

-That as the database is considerable and yet has failed to demonstrate efficacy, that a brief summary of the 2 placebo controlled trials is included in Section 5.1.

SmPC – PL – Labeling comments

Section 4.1 (Therapeutic indications):

We endorse the conclusions of the Rapporteur that no change should be made to the current text.

Section 4.2 (Posology and method of administration):

We endorse the conclusions of the Rapporteur and endorse the text proposed which is:-

Children:

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children. Therefore,

Detrusitol/Detrusitol SR is not recommended for children.

Section 4.8 (Undesirable effects):

We propose that those adverse effects which have been observed more frequently in children treated with tolterodine than placebo (i.e urinary tract infections, diarrhoea and abnormal or hyperactive behaviour]) are incorporated into this section. We propose the following text:-
“In 2 paediatric phase 3 randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 pediatric patients (486 on tolterodine extended release capsules and 224 on placebo) were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infections: tolterodine 6.6% ; placebo 3.6%, diarrhoea: tolterodine 3.3% ; placebo 0.9% , abnormal behaviour: tolterodine 1.6% ; placebo 0.4%)”.

Section 5.1 (Pharmacodynamic properties):

We propose that as the database is considerable and yet has failed to demonstrate efficacy, that a brief summary of the placebo controlled trials is included in Section 5.1. We propose the following text:-

“Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 pediatric patients (486 on DETROL LA and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied.”

Comments from MS:

As stated by the rapporteur, the placebo controlled studies (020 and 008) could not demonstrate a clinically significant effect of tolterodine for the treatment of symptoms of urge incontinence/overactive bladder syndrome in children 5 to 10 years old. The etiological background for the incontinence in the children selected for the studies is unclear. Moreover, the safety analysis showed a slightly higher rate of gastrointestinal adverse events, urinary tract infections, elevated post-void residual urinary volumes and abnormal behaviours in children treated with tolterodine. In this context, France is of the opinion that the lack of efficacy in children should be reflected in the SPC and that a summary of the results from the placebo controlled studies should be added in section 5.1 of the SmPC.

With regard to the pharmacokinetic results obtained in children and proposed to be added by the rapporteur in section 5.2, we consider that the statement should be deleted. In fact, the studies involved more or less patients. The results are debatable, not of a real interest and could wrongly encourage potential prescribers (see below).

SmPC : Comments on the rapporteur's proposal

Section 4.2 Posology and method of administration

The following modification should be implemented :

‘Children

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children (see section 5.1). Therefore, Detrusitol/Detrusitol SR is not recommended for children’.

Section 5.1 Pharmacodynamic properties

The following statement should be added :

‘Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12-week studies were conducted using tolterodine extended release capsules. No significant difference in the two groups were observed with regard to the primary objective (change from baseline in total number of incontinence episodes/week). Moreover, the safety analysis showed a slightly higher rate of gastrointestinal adverse events, urinary track infections, elevated post-void residual urinary volumes and abnormal behaviours in children treated with tolterodine.’

Section 5.2 Pharmacokinetic properties

The proposed statement should be deleted

“Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults.”

Comments from MS:

As there was no Co-Rapporteur’s assessment, only the Rapporteur’s AR can be commented upon.

MS fully endorses the conclusions of the Rapporteur.

RMS proposal

In line with comments received from member states, the Rapporteur proposes the following text to be included in the SPC of Detrusitol, Detrusitol SR, Protol SR, Detsel:

Section 4.2 (Posology and method of administration):

-

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children (see section 5.1). Therefore, Detrusitol/Detrusitol SR is not recommended for children.

Section 4.8 (Undesirable effects):

“In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infections: tolterodine 6.6% ; placebo 3.6%, diarrhoea: tolterodine 3.3% ; placebo 0.9%, abnormal behaviour: tolterodine 1.6% ; placebo 0.4%”).

Section 5.1 (Pharmacodynamic properties):

- ‘Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12-week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference in the two groups was observed with regard to the primary objective (change from baseline in total number of incontinence episodes/week).’

Section 5.2 Pharmacokinetic properties

We would like to keep the proposed text as there are no severe safety concerns related to use in children. A cross-reference to section 4.2 and 5.1 could be included to make sure the prescriber has the full set of information.

“Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults, (see Sections 4.2 and 5.1).”

VI. MAH RESPONSE ON THE PROPOSED SPC TEXT:

1) Pfizer accepts the text proposed by the rapporteur for section 4.2 as out-lined below.

Section 4.2 (Posology and method of administration):

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children (See section 5.1). Therefore, Detrusitol/Detrusitol SR is not recommended for children.

2) Pfizer accepts the text proposed by the rapporteur for section 4.8 with minor proposed amendments as out-lined below. Please note that the incidence of urinary tract infections for

tolterodine, as stated in Table 3 of the assessment report is 6.8 % and not 6.6 %. Pfizer have therefore, corrected this typographical error in the proposed text.

Section 4.8 (Undesirable effects):

*In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine ~~6.6%~~ **6.8 %**; placebo 3.6 %, diarrhoea: tolterodine 3.3 %; placebo 0.9 % abnormal behaviour: tolterodine 1.6 %; placebo 0.4 %). (See section 5.1)*

3) Pfizer accepts the text proposed by the rapporteur for section 5.1 with minor proposed amendments out-lined below to increase the clarity of the information provided.

Section 5.1 (Pharmacodynamic Properties):

*Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed **in either study** with regard to ~~the primary objective~~ (change from baseline in total number of incontinence episodes/week). (See section 4.8)*

4) Pfizer accepts the text proposed by the rapporteur for section 5.2 as out-lined below.

Section 5.2 (Pharmacokinetic Properties):

Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (See sections 4.2 and 5.1).

Rapporteur's Comment

The MAH has basically accepted the proposed changes in the SPC and only made small amendments in sections 4.8 (correction to 6,8%) and in section 5.1. Those changes are acceptable, and as a consequence the following text should be included in section 5.1:

*Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed **in either study** with regard to ~~the primary objective~~ (change from baseline in total number of incontinence episodes/week). (See section 4.8)*

VII. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rapporteur's conclusion: The applicant has submitted several pharmacokinetic as well as efficacy and safety studies investigating detrusitol in the paediatric population. The pharmacokinetics is quite well studied and this will now be reflected in the SPC. The placebo controlled studies could not convincingly demonstrate a clinically meaningful effect of tolterodine for the treatment of symptoms of urge incontinence/overactive bladder syndrome in children 5 to 10 years old. Neither were any studies provided

that could demonstrate a clinical effect in paediatric patients with neurologic bladder disorders. The small effects of tolterodine reported in studies 020 and 008 on bladder storage capacity are not considered clinically meaningful in this population.

The target patient population for tolterodine treatment are patients suffering from symptoms of overactive bladder syndrome (OAB), a clinical condition with an unknown etiology that becomes increasingly common with age and occurs most often in postmenopausal women. It is uncertain whether a similar condition exists in children and, if so, it could be assumed that possible etiological factors in children differ substantially from those behind OAB in adult and ageing patients. Therefore, it is unlikely that pharmacokinetic results obtained in children can be extrapolated to also reflect a clinical effect in children. In order to theoretically justify further clinical trials with tolterodine in paediatric patients, it is proposed that the clinical condition be carefully described and well defined in children, for example as neurologic bladder disorder, urogenital malformations or other conditions that could be described in detail by use of micturition diaries etc, and that such patient groups are studied separately in large enough controlled studies.

The safety analysis showed a slightly higher rate of gastrointestinal AEs, UTI, post-void residual urinary volume and abnormal behaviour in children treated with tolterodine.

It is suggested that the SPC changes should be implemented in the MS using variation procedures.

Based on the review, the paediatric data should lead to the inclusion of the following SPC text:

4.2 (Posology and method of administration):

Efficacy of Detrusitol/Detrusitol SR has not been demonstrated in children (See section 5.1). Therefore, Detrusitol/Detrusitol SR is not recommended for children.

4.8 (Undesirable effects):

In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine 6.8 %; placebo 3.6 %, diarrhoea: tolterodine 3.3 %; placebo 0.9 % abnormal behaviour: tolterodine 1.6 %; placebo 0.4 %). (See section 5.1)

5.1 (Pharmacodynamic Properties):

Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double-blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed in either study with regard to (change from baseline in total number of incontinence episodes/week). (See section 4.8)

5.2 (Pharmacokinetic Properties):

Children

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (See sections 4.2 and 5.1).