

MEMORANDUM

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

DATE: March 16, 2005

FROM: Paula Gish, R.Ph. Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, M.D., MPH., Team Leader
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review;
PID #D040002
Drug: Tolterodine (Detrol® and Detrol® LA, NDAs 020771 & 021228)
Pediatric Exclusivity Approval Date: January 5, 2004

I. Executive Summary

The AERS database was searched for reports of adverse events occurring with the use of tolterodine in pediatric patients. Overall, AERS contains 8653 cases for all Detrol® and Detrol® LA products (raw count, all ages, foreign and domestic, as well as those with null values for age and country of origin). Thirty-one of the 8653 cases were pediatric cases, representing 29 unduplicated cases since approval. These cases were reviewed in a previous consult at the request of the Division of Reproductive and Urologic Drug Products in March of 2004.¹ The reports primarily involved anticholinergic and CNS stimulation events that were transient or abated upon tolterodine discontinuation.

This consult focused on pediatric AERS reports received during the 1-year period following the approval of pediatric exclusivity, 01/05/2004 to 02/05/2005 (referred to hereafter as the *pediatric exclusivity period*). We used an AERS “cut-off” date of 02/05/2005 to allow an additional month for all reports received by 01/05/2005 to be entered into AERS. During the pediatric exclusivity period a total of 166 cases were received (raw count, all ages, foreign and domestic, as well as those with null values for age and country of origin). None of the 166 cases were pediatric reports. No new safety concerns were identified as a result of this review. We will continue routine monitoring of adverse events in pediatric patients.

¹ Gish P, Overview of AERS data for pediatric patients (ages 0-16 years), March 17, 2004 (DFS March 18, 2004). See Appendix 2.

II. AERS Search Results: Tolterodine

AERS was searched on March 7, 2005 for reports listing tolterodine as a suspect drug. The search included all sources, foreign and domestic. In the tables below, the US counts are in parenthesis.

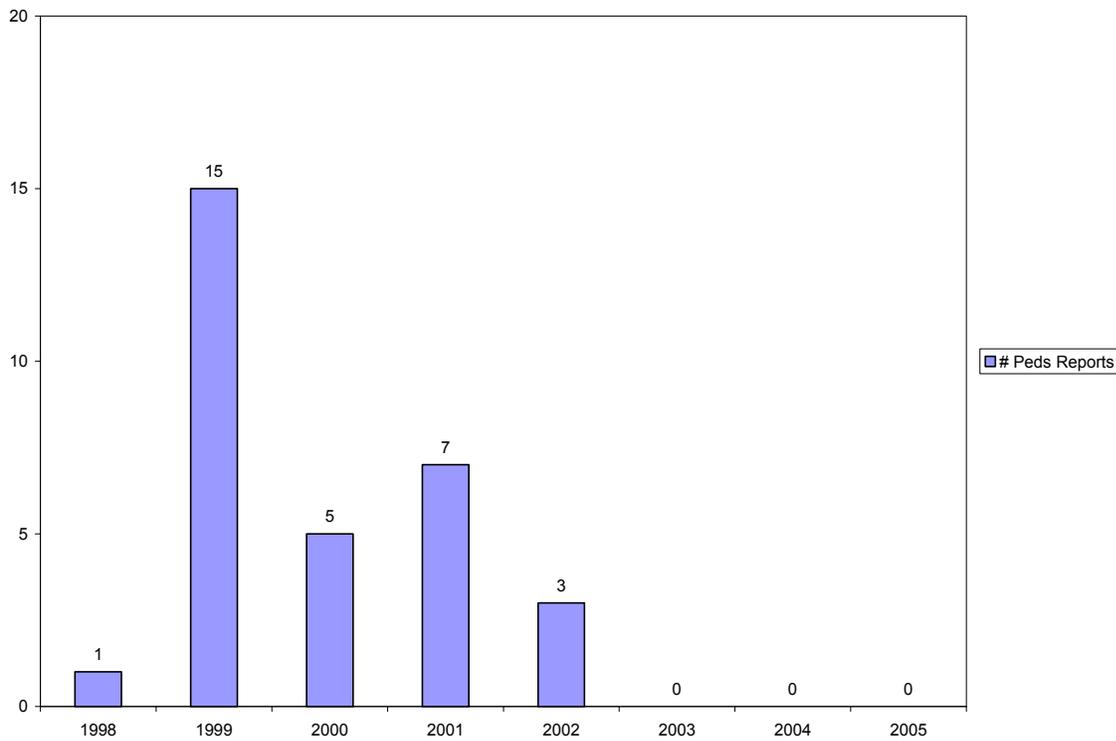
A. From approval date (03/25/98) through AERS cut-off date (02/05/2005)

1. Raw Counts of Reports

Table 1. Raw counts¹ of total tolterodine reports from approval date through cut-off date of February 5, 2005 (U.S. counts in parenthesis)			
	All reports since approval (US)	Serious ² (US)	Death (US)
All ages ³	8653 (8286)	1688 (1344)	43 (24)
Adults (17+)	2608 (2318)	1296 (1018)	36 (18)
Peds (0-16)	31 (25)	18 (12)	0 (0)

¹ May include duplicate reports.
² Serious outcomes per regulatory definition, which included death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
³ Includes null ages.

Figure 1: Reporting trend for pediatric reports since approval:



Top 20 reported event Preferred Terms and labeling status of these events (underlined denotes unlabeled events):

Table 2: Counts¹ of top 20 reported events (Preferred Terms) from approval to 02/05/2005		
	Preferred Term	Raw Count
All Ages	Dry Mouth	1772
	<u>Drug Ineffective</u>	1584
	Constipation	675
	Headache	647
	Dizziness	525
	<u>Urinary Incontinence</u>	502
	Keratoconjunctivitis Sicca	384
	<u>Pollakiuria</u>	364
	<u>Nausea</u>	343
	Oedema Peripheral	335
	<u>Condition Aggravated</u>	320
	<u>Drug interaction</u>	270
	Vision Blurred	264
	<u>Insomnia</u>	263
	Dysuria	242
	Dyspepsia	230
	Fatigue	222
	<u>Micturition Urgency</u>	221
	<u>Drug Effect Decreased</u>	199
	<u>Diarrhoea</u> (Detrol: labeled, Detrol LA:unlabeled)	190
Sedation	185	
Adults (17+ years)	Dry mouth	577
	<u>Drug Ineffective</u>	307
	Headache	238
	Constipation	229
	Dizziness	229
	<u>Urinary Incontinence</u>	152
	Keratoconjunctivitis Sicca	143
	<u>Nausea</u>	132
	<u>Condition Aggravated</u>	126
	<u>Pollakiuria</u>	124
	Oedema Peripheral	114
	<u>Drug Interaction</u>	109
	Vision Blurred	107
	<u>Insomnia</u>	100
	Fatigue	89
	Dysuria	87
	Dyspepsia	86
	Micturition Urgency	76
	Urinary Retention	73
	<u>Confusional State</u>	71
<u>Diarrhoea</u> (Detrol:labeled, Detrol LA:unlabeled)	69	
Pediatrics (0-16 years)	<u>Aggression</u> (Detrol:unlabeled, Detrol LA:labeled)	3
	Fatigue	3

	Headache	3
	<u>Medication Error</u>	3
	Constipation	2
	<u>Dermatitis</u>	2
	Dizziness	2
	<u>Drug Interaction</u>	2
	Dysuria	2
	<u>Insomnia</u>	2
	<u>Irritability</u>	2
	<u>Pruritis</u>	2
	<u>Psychomotor Hyperactivity</u> (Detrol:unlabeled, Detrol LA:labeled)	2
	Urinary Retention	2
	Vision Blurred	2
	Abdominal Pain	1
¹ Raw counts: may include terms from duplicate reports		

B. From pediatric exclusivity approval date (01/05/2004) through AERS cut-off date (02/05/2005)

1. Raw Counts of Reports

Table 3: Raw counts¹ of total tolterodine reports for pediatric exclusivity period: 01/05/2004 – 02/05/2005 (U.S. counts in parenthesis)			
	All reports 01/05/2004 to 02/05/2005(US)	Serious ² (US)	Death (US)
All ages ³	166 (123)	159 (116)	7 (5)
Adults (17+)	134 (97)	129 (92)	5 (3)
Peds (0-16)	0 (0)	0 (0)	0 (0)
¹ May include duplicate reports.			
² Serious outcomes per regulatory definition, which included death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.			
³ Includes null ages.			

2. Top 20 reported event Preferred Terms and labeling status of these events (underlined denotes unlabeled events):

Table 4: Counts¹ of top 20 reported events (Preferred Terms) for pediatric exclusivity period: 01/05/2004 - 02/05/2005		
	Preferred Term	Raw Count
All Ages	<u>Drug Ineffective</u>	23
	Dry Mouth	16
	<u>Dyspnoea</u>	11
	Constipation	10

	<u>Pollakiuria</u>	10
	<u>Urinary Incontinence</u>	10
	<u>Condition Aggravated</u>	9
	<u>Fall</u>	9
	Urinary Retention	9
	<u>Bladder Disorder</u>	8
	<u>Cerebrovascular Accident</u>	8
	Dizziness	8
	Headache	8
	Abdominal Pain	7
	<u>Confusional State</u>	6
	<u>Diarrhoea (Detrol:labeled, Detrol LA:unlabeled)</u>	6
	<u>Drug Effect Decreased</u>	6
	Dysuria	6
	<u>Medication Error</u>	6
	<u>Nausea</u>	6
	<u>Nocturia</u>	6
Adults (17+ years)	<u>Drug Ineffective</u>	18
	Dry Mouth	13
	<u>Dyspnoea</u>	10
	<u>Pollakiuria</u>	10
	<u>Urinary Incontinence</u>	10
	<u>Condition Aggravated</u>	9
	Constipation	9
	<u>Fall</u>	9
	Headache	8
	Urinary Retention	7
	<u>Bladder Disorder</u>	6
	<u>Cerebrovascular Accident</u>	6
	<u>Confusional State</u>	6
	<u>Diarrhoea (Detrol:labeled, Detrol LA:unlabeled)</u>	6
	Dizziness	6
	<u>Drug Effect Decreased</u>	6
	Dysuria	6
	<u>Nausea</u>	6
	<u>Nocturia</u>	6
	<u>Pain In Extremity</u>	6
	<u>Weight Decreased</u>	6
Pediatrics (0-16 years)	N/A	N/A
¹ Raw counts: may include terms from duplicate reports		

III. Postmarketing Hands-On Review of All Pediatric Adverse Event Reports Received During Pediatric Exclusivity Period (January 5, 2004 – February 5, 2005)

- A. Demographic characteristics of pediatric cases received during the pediatric exclusivity period

No pediatric reports were received during the pediatric exclusivity period.

- B. Labeling status of the top 20 reported adverse events and comparison to adult adverse event profile during the pediatric exclusivity period

No pediatric reports were received during the pediatric exclusivity period.

- C. Description of fatal and life-threatening pediatric cases

There were no fatalities or life-threatening pediatric cases reported during the pediatric exclusivity period.

- D. Summary of all pediatric reports

All pediatric AERS reports received since approval (specifically from 03/25/1998 to 03/02/3004) were reviewed in a previous consult at the request of the Division of Reproductive and Urologic Drug Products in March of 2004 (see Appendix 2). The 29 unduplicated reports primarily involved anticholinergic and CNS stimulation events (paradoxical agitation) that were transient or abated upon tolterodine discontinuation. Tolterodine is a muscarinic receptor antagonist, and therefore, anticholinergic effects are expected. The consult recommended that the potential for pediatric patients to develop paradoxical agitation be included in the labeling for Detrol and Detrol LA in addition to several currently unlabeled anticholinergic effects (confusion, overheating, and flushing).

This review of pediatric adverse events focused on the 1-year period following approval of pediatric exclusivity, specifically 01/05/2004 to 02/05/2005. No pediatric reports were received during the pediatric exclusivity period. No new safety concerns were identified as a result of this review.

IV. Summary

This review of pediatric adverse events focused on the 1-year period following approval of pediatric exclusivity with an additional month for the cases to be entered into AERS, specifically 01/05/2004 to 02/05/2005. No pediatric reports were received during the exclusivity period. No new safety concerns were identified as a result of this review. We will continue routine monitoring of adverse events in pediatric patients.

_____/s/ Paula Gish/3-16-05
Paula Gish, Safety Evaluator

Concur:

_____/s/ Melissa Truffa/3-16-05
Melissa Truffa, Team Leader

Appendix 1

Drug Product Information

The labeling for Detrol® and Detrol® LA can be accessed at:

http://www.pfizer.com/do/medicines/mn_uspi.html

Relevant Pediatric Labeling:

Detrol (tolterodine tartrate tablets)

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pediatric: The pharmacokinetics of tolterodine have not been established in pediatric patients.

PEDIATRIC USE

The safety and effectiveness of DETROL in pediatric patients have not been established.

Detrol LA(tolterodine tartrate extended release capsules)

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pediatric: Efficacy in the pediatric population has not been demonstrated.

The pharmacokinetics of tolterodine extended release capsules have been evaluated in pediatric patients ranging in age from 11-15 years. The dose-plasma concentration relationship was linear over the range of doses assessed. Parent/metabolite ratios differed according to CYP2D6 metabolizer status: EMs had low serum concentrations of tolterodine and high concentrations of the active 5-hydroxymethyl metabolite, while PMs had high concentrations of tolterodine and negligible active metabolite concentrations.

PEDIATRIC USE

Efficacy in the pediatric population has not been demonstrated.

A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. 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 behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Appendix 2

<p align="center">DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</p>		<p align="center">ODS POSTMARKETING SAFETY REVIEW</p>	
<p>TO: Daniel Shames, M.D., Director Division of Reproductive and Urologic Drug Products (DRUDP) HFD-580</p>		<p>FROM: Paula Gish, R.Ph. Safety Evaluator, DDRE HFD-430</p>	<p>PID #: D040136 DATE: March 17, 2004</p>
<p>DATE REQUESTED: 3/2/04</p>		<p>REQUESTOR/Phone #: Lisa Soule, M.D.</p>	
<p>DRUG (Generic): tolterodine</p>		<p>NDA/IND #20-771, 21-228</p>	<p>SPONSOR: Pfizer</p>
<p>DRUG NAME (Trade): Detrol®, Detrol® LA</p>		<p>THERAPEUTIC CLASSIFICATION: Genitourinary</p>	
<p>EVENT: Overview of AERS data for pediatric patients (ages 0-16 years)</p>			
<p>Introduction/Executive Summary: Detrol and Detrol LA were granted pediatric exclusivity on January 5, 2004. In October 2003, an efficacy supplement was submitted by Pfizer to add pharmacokinetic data and adverse event data from pediatric clinical trials to the labeling for Detrol LA. This review of the Adverse Event Reporting System (AERS) for pediatric adverse events in association with Detrol and Detrol LA was requested to assist DRUDP in the review of Pfizer's proposed labeling changes.</p> <p>AERS was searched on March 2, 2004 for adverse events associated with the use of tolterodine for pediatric patients ages 0-16 years. A total of 29 unduplicated cases were retrieved.</p> <p>The majority of the cases were nonserious however there were 5 hospitalizations. Of these only one appeared plausibly related to tolterodine (breathing difficulties, nocturnal laryngitis and coughing). The remaining 4 hospitalizations (transient blindness, heartblock, exfoliative rash, convulsions) were unlikely related to tolterodine due to negative dechallenges or underlying conditions. In addition, two urinary tract infections were reported but both appear related to an underlying condition and not to tolterodine therapy.</p> <p>Most cases reported anticholinergic and CNS stimulation events that abated upon tolterodine discontinuation or were transient (tolterodine therapy continued and the event resolved). Tolterodine is a muscarinic receptor antagonist, and therefore, anticholinergic effects are expected. However, some anticholinergic effects reported for pediatric patients are currently unlabeled (confusion, overheating, flushing).</p> <p>Ten cases (6 male, 4 female) reported events associated with CNS stimulation (aggression, hyperactivity, insomnia). Two patients (both males) had histories of attention deficit hyperactivity disorder (ADHD). One patient with a history of ADHD experienced hyperactivity that abated upon tolterodine discontinuation and reappeared after tolterodine was reintroduced (increasing the likelihood of attribution to tolterodine). CNS stimulation with antimuscarinic agents is thought to be a result of anticholinergic effects. Although anticholinergic effects are usually sedating, physostigmine, a cholinesterase inhibitor that prolongs the action of acetylcholine, is often successful in reversing paradoxical stimulation reactions. Children and the elderly are more susceptible to paradoxical agitation reactions.² Presently, paradoxical agitation events are not included in the labeling and are not included in the changes submitted by Pfizer.</p> <p>The potential for pediatric patients to develop paradoxical agitation should be included in the labeling for Detrol and Detrol LA in addition to the currently unlabeled anticholinergic effects (confusion, overheating, and flushing).</p>			

² Kit L, Cheng BS, et al. Paradoxical Excitation with diphenhydramine in an adult. *Pharmacotherapy* 1997; 17(6): 1311-1314.

Relevant Product Labeling:

DESCRIPTION: Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

Pediatric Use: The safety and effectiveness of tolterodine in pediatric patients has not been established.

ADVERSE REACTIONS

Detrol clinical trials: The most common adverse events reported by patients receiving DETROL were dry mouth, headache, constipation, vertigo/dizziness, and abdominal pain. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are expected side effects of antimuscarinic agents.

Detrol LA clinical trials: The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents.

Search Date: 3/2/04

Search Type(s): AERS Literature Other

AERS Search Criteria:

Drug Names: tolterodine, Detrol, Detrol LA

Adverse events: all events for patients 0-16 years of age.

AERS Search Results/Summary of Data

The search identified a total of 29 unduplicated cases for patients ages 0-16 years (a table of cases is attached).

Demographics for the AERS data (n=29)

Age: Mean = 9 years (range, 11 months to 16 years)

Gender: 19 females and 8 males

Location: US cases = 24 Non-US = 5

Outcome: 0- deaths, 5- Hospitalizations, 1- Disability

Positive Dechallenge: 15

Positive Rechallenge: 1

Indication: incontinence (7), frequent urination (4), unknown (4), overactive bladder (3), no indication/accidental ingestion (3), nocturnal enuresis (2), overactive bladder/dysfunctional voiding (1), dysfunctional voiding (1), bladder spasms (1), vesical instability (1), spastic bladder, grade II ureter reflux (1), and stress incontinence (1)

The majority of patients were treated with Detrol tablets (25) versus Detrol LA capsules (4). Twenty-one cases reported dosing information: 1mg/day (2), 2mg/day (13), 4mg/day (5), 6mg/day (1).

Age (# cases):

<2 yrs (1)
2-5 yrs (4)
6-11 yrs (16)
12-16 yrs (8)

Dose range by age group

dose unknown
2 mg/day (dose unknown in 2 of 4 cases)
1 mg- 4 mg/day (dose unknown in 3 of 16 cases)
2 mg-6 mg/day (dose unknown in 2 of 8 cases)

The 6 cases with a serious outcome of hospitalization (5) or disability (1) are summarized below:

- Three months after beginning tolterodine therapy a ten-year-old female experienced transient blindness episodes lasting for 1 hour on a daily basis (the report did not indicate if this was temporally associated with administration of Detrol). The blindness episodes continued after tolterodine was discontinued.
- A 12-year-old female experienced heart block, dizziness, chest pain and fatigue while treated with tolterodine and azathioprine. Tolterodine was discontinued. The heart block resolved, but dizziness, chest pain did not resolve.
- A 7-year-old female developed a blistering, exfoliative skin rash two days after beginning tolterodine and loratadine therapy. Follow-up information revealed positive culture for Herpes Simplex Type I.
- A five-year-old female with no prior seizure history experienced a seizure while treated with tolterodine (time to onset unknown). Follow-up information indicated the patient was being treated with Tegretol, phenobarbital and Diastat suppositories.
- An 8-year-old female experienced breathing difficulties, nocturnal laryngitis and coughing 5 days after beginning tolterodine treatment. The events abated after tolterodine was discontinued.
- A 9-year-old female experienced hyperactivity during tolterodine therapy. The dose was decreased to 2mg daily, and then discontinued. The report did not state if the event abated after tolterodine was discontinued. (*reported outcome: disability*)

Three of the 29 cases reported medication errors. Two reported that Detrol was mistakenly dispensed in place of another medication (DDAVP- 1 case, unknown medication - 1 case). In the third case it was not known if a Detrol suspension had been prepared correctly (unclear if medication error had occurred).

Of the 29 cases, 9 reported events associated with anticholinergic effects (confusion, lethargy, urinary/fluid retention, overheating, constipation, flushing, dry mouth, and blurry vision), 8 reported events associated with paradoxical stimulation of the central nervous system (aggression, hyperactivity, irritability, sleepwalking, jerky movement, insomnia) and 2 reported both types of events.

Two cases reporting anticholinergic-type events also reported bladder infections. An 8-year-old female experienced lethargy, back pain, memory impairment and loss of appetite after treatment with 2 doses of Detrol LA for overactive bladder. Detrol LA was discontinued and the events abated. One week after tolterodine discontinuation the patient was diagnosed with a bladder infection. The physician reported the urinary tract infection (UTI) was due to poor, inefficient bladder emptying and did not suspect Detrol LA as the cause of the UTI. In a second case a 9-year-old female experienced blurry vision, nausea and equilibrium problems 4 days after beginning treatment with Detrol 1mg twice a day. Subsequently, the patient was taught self-catheterization and to administer 2mg crushed tolterodine intravesicularly every 12 hours. The patient developed a UTI. The emergency room physician did not attribute the UTI to Detrol. The patient continues with Detrol intravesicularly.

Most of the 19 events associated with anticholinergic effects (including CNS stimulation) reported a time to onset of a few days (range: 1 day to 1 month) and abated upon tolterodine discontinuation, or were transient (patient continued tolterodine therapy and event resolved). One case (hyperactivity) reported a positive rechallenge. Three cases (exfoliative rash, dyspnea/laryngitis/cough, diaphoresis) reported the events abated upon discontinuation of tolterodine. Three cases (transient blindness, heart block/dizziness/chest pain, strong urine odor) did not resolve or only partially resolved upon tolterodine discontinuation. The remaining 4 cases (convulsions, menstrual cycle changes, decreased effect of fluoxetine, accidental exposure) did not provide dechallenge/rechallenge information.

Discussion: Five hospitalizations were reported, however only one appeared plausibly related to tolterodine (breathing difficulties, nocturnal laryngitis and coughing). The events began after several days of tolterodine therapy and abated upon tolterodine discontinuation. The events may be related to anticholinergic effects on mucous membranes. The remaining hospitalizations were unlikely related to tolterodine due to negative

dechallenges (amaurosis fugax, chest pain/dizziness) or underlying conditions (herpes). The patient who experienced a convulsion while treated with tolterodine was later placed on anticonvulsant therapy. This suggests another etiology may be suspected.

The two urinary tract infections appear related to an underlying condition and not to tolterodine therapy. In one case only two doses of Detrol were administered and a UTI was diagnosed a week later. The physician attributed the UTI to underlying poor, inefficient bladder emptying and not to tolterodine. In the second case the patient's recent self-catheterization is the more likely cause of the UTI.

Most of the cases reported anticholinergic and CNS stimulation events that abated upon tolterodine discontinuation or were transient (tolterodine therapy continued and the event resolved). Tolterodine is a muscarinic receptor antagonist and anticholinergic effects are expected. Presently, some anticholinergic effects reported for pediatric patients are included in the labeling: dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and headaches. However, other anticholinergic events reported in AERS for pediatric patients are not included in the labeling (confusion, overheating, flushing).

A striking number of cases (10) reported events associated with CNS stimulation: aggression, hyperactivity, irritability, insomnia. Six were in males and four were in females with an average patient age of 10 years (range 5 to 16 years). Six (all in males) reported the events abated after tolterodine discontinuation. The 4 remaining cases (all in females) did not provide dechallenge information. Two patients (both males) had a history of Attention Deficit Hyperactivity Disorder (ADHD) and were treated concomitantly with Ritalin. One of the patients with a history of ADHD developed hyperactivity that abated upon tolterodine discontinuation and reappeared after tolterodine was reintroduced (increasing the likelihood of attribution to tolterodine). CNS stimulation responses have been attributed to anticholinergic effects. Although anticholinergic effects are usually sedating, physostigmine, a cholinesterase agent, is often successful in reversing paradoxical reactions associated with anticholinergic agents. Children and the elderly more susceptible to paradoxical agitation reactions.² Presently, paradoxical agitation events are not included in the labeling and are not included in the changes submitted by Pfizer.

Conclusion: Most of the cases reported anticholinergic and CNS stimulation events that were reversible or transient. Presently, paradoxical agitation events are not included in the labeling and are not included in the changes submitted by Pfizer. The potential for pediatric patients to develop paradoxical agitation events such as aggression, hyperactivity, irritability, and insomnia should be added to the labeling for Detrol and Detrol LA in addition to the currently unlabeled anticholinergic events (confusion, overheating, flushing).

References:

Reviewer's Signature / Date:

Team Leader's Signature / Date:

Division Director Signature / Date:

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
1 3694143 2001060458US	Unk gender/11 mos USA	Unknown Unknown	Constipation	Unknown Hx: bladder repair	Previously treated with Ditropan, switched to Detrol LA after bladder surgery. Treated with lactulose and prune juice
2 3651842 2001042604US	Female/2 years USA	Unknown Unknown	Possible accidental exposure of one Detrol LA capsule	Unknown Hx: Unknown	No adverse event reported, inquiry about accidental ingestion
3 3304003 852/20771	Female/ 5 years USA	2mg/day 6 days	Headache Bothersome eyes Rash/Hives Flushed cheeks	Phenazopyridine Hx: None	Symptoms disappeared after Detrol was D/C'd and Benadryl was given for the rash
4 3598730 2000032072US	Female/5 years USA	Unknown < 1 week	Increased aggression	Unknown Hx: Unknown	Very little information provided.

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
5 3788485 2002102611US	Female/5 years USA	1mg bid Unknown	Possible med error Convulsions Hospitalization	Acetaminophen Diphenhydramine Pseudophedrine Hx: Unknown	Suspension may have been prepared incorrectly – possible accidental overdose Follow-up: pt now on therapy with Tegretol, phenobarbital and Diastat suppository
6 3652561 2000037887US	Female/6 years USA	1mg bid 2 days	Micturition urgency Pruritis Dysuria	Unknown Hx: overactive bladder	Events resolved after Detrol was discontinued
7 3358054 9042/20771	Female/7 years United Kingdom	1 mg BID 2 days	Herpes type I rash w/exfoliation Hospitalization	Loratadine Unspecified med Hx: tonsillitis, hay fever, seizures w/Amoxicillin, Penicillin allergy	Physician commented rash was most likely due to herpes and not caused by Detrol
8 3384131 8481/20771	Female/7 years USA	4mg qpm < 1mos	Medication error Strong urine odor Headache	Unknown Hx: Unknown	Detrol dispensed by mistake Headache resolved, but Odor persists after Detrol discontinued

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
9 3390811 8613/20771	Male/8 years USA	2mg BID < 2 weeks	Dry mouth Hyperactivity Inability to focus	Ritalin Hx: honor student, ADHD, incontinence after many surgeries to correct classic bladder	Positive rechallenge for hyperactivity and inability to focus
10 3695312 2001053589US	Female/8 years USA	4mg qd 1 day	Bladder infection Lethargy Drug interaction Back pain Memory impairment Loss of appetite	Phenytoin Amoxicillin Hx: convulsions	Detrol LA DC'd, events abated after 1 week. Physician reported UTI consistent with poor, inefficient bladder emptying and does not suspect Detrol LA as the cause
11 3817618 2002113550BE	Female/8 years Belgium	Unknown 5 days	Nocturnal laryngitis Dyspnea Cough Hospitalization	Unknown Hx: Unknown	Events abated after Detrol discontinuation

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
12 3205069 5406/20771	Female/9 years United Kingdom	1mg qd 3 months	Amaurosis Fugax Hospitalization	Lactulose, senna, buresonide inhalation, terbutaline inhalation Hx: NKA, asthma, constipation, migraine, prior Oxybutynin use, enuresis	Temp blindness in left eye lasting for 1 hour on a daily basis, MRI normal, MRI angiography normal, Ophthalmic exam normal, Detrol DC'd but event continues
13 3298167 3595/20771	Female/ 9 years USA	1mg BIDx11 days 4-5 days Restarted: 2mg BID intravesicularly 12 days	Blurry vision Nausea Equilibrium problems Bladder infection Dysuria Hematuria	None Hx: small bladder, allergic rxn to Ditropan, Levsin use resulted in nosebleeds, Tofranil therapy failed	Experienced blurry vision, nausea, equilibrium problems. Subsequently switched to intravesicular administration. Later developed bladder infection – not attributed to Detrol by ER physician.
14 3311640 7533/20771	Male/ 9 years USA	1mg qhs 4 days	“Got Mean” Agitation	Unknown Hx: lack of effect with previous Ditropan therapy	Event abated after Detrol was discontinued

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
15 3399784 1999005106NL	Female/9 years Netherlands	1mg QID (4mg/day) Unknown	Hyperactivity Excited Disability	Sulfa TMP Augmentin Nitrofurantoin Hx: Unknown	Detrol dose lowered to 1mg/BID, then d/c'd, dechallenge info unknown
16 3522588 2000008605US	Female/9 years USA	Unknown Unknown	Drug interaction with Prozac	Unknown Hx: vesico-ureteric reflux	Prozac became less effective after beginning Detrol therapy
17 3548951 2000022548US	Male/9 years USA	2mg qd unknown	Confusion	Unknown Hx: Unknown	Recently increased dosage from 1mg to 2mg/day, event abated after dosage decreased
18 3569075 2000027251US	Unk gender/9 years USA	1mg bid < 3 mos	Increased insomnia	Levocarnitine Hx: Unknown	Possibly related to emotional stress, patient remains on Detrol

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
19 3498883 1999003261US	Male/10 years USA	2mg qd 2 weeks	Jerky movement	Unknown Hx: Unknown	“Motor tick” abated upon Detrol discontinuation
20 3548458 2000020855US	Female/10 years USA	Unknown <15 days	Red face Tired Patchy dry skin Syncope Overheating Thirsty Feels warm	Fluvoxamine Clonidine Hx: Depression	Events abated slowly – over 2 weeks after discontinuation of Detrol
21 3311641 7534/20771	Male/ 11 years USA	2mg qhs 6 days	“Got Mean” Aggression	Unknown Hx: previous Ditropan therapy associated with lack of effect	Event abated after Detrol was discontinued
22 3275080 5410/20771	Female/12 years USA	2mg BID 1 month	Tired Retaining Fluid	None Hx: incontinence w/ laughing, coughing	Events resolved, pt continues on Detrol 2mg BID

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
23 3312232 7862/20771	Male/12 years USA	1mg BID 2 days	Diaphoretic	Unknown Hx: None	Event abated after Detrol was discontinued
24 3316839 8357/20771	Female/12 years United Kingdom	1mg BID < 6 mos	Heart block Dizziness Chest pain Fatigue Hospitalization	Prednisolone Azathioprine Kapsovit Omeprazole Gaviscon Paracetamol Hx: None (?)	Hospitalized due to varying degree of heart block, heart block is resolved, however dizziness, chest pain, fatigue are unresolved
25 3311643 7535/20771	Male/13 years USA	2mg qhs 4 days	Felt nervous and “crabby” Irritability Nervousness	None Hx: previous Ditropan therapy associated with lack of effect	Events abated after Detrol discontinued
26 3695479 2001058284US	Female/14 years USA	Unknown < 3 weeks	Headache	Unknown Hx: neurogenic bowel/bladder, Bladder catheter	Detrol LA Very little information provided.

TABLE 1 – adverse events for ages 0-16 years: tolterodine (Detrol, Detrol LA)

CASE # MFR REPORT #	SEX/AGE/ LOCATION	DOSE/ TIME TO ONSET	ADVERSE EVENT/ OUTCOME	CONCOMITANT DRUGS/MEDICAL HISTORY	COMMENT
27 3495663 199904713US	Female/15 years USA	2mg qd 6 days	Sleepwalking	Cetirizine Nasalcrom Hx: cough, multiple allergies	Continued to take Detrol, events resolved
28 3312288 7358/20771	Male/16 years USA	6mg/day “couple weeks”	Medication error Trouble sleeping Fighting w/other children Aggression Urinary retention	Ritalin Hx: Head trauma, ADHD, enuresis	Inadvertently dispensed Detrol instead of DDAVP Urinary retention resolved after Detrol was discontinued
29 3394867 8604/20771	Female/16 years USA	Unknown Unknown	Abdominal pain Menstrual cycle changes	Unknown Hx: Unknown	Stopped taking Detrol, dechallenge info unknown

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this page is the manifestation of the electronic signature.**

/s/

Paula Gish
3/21/05 03:25:09 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/21/05 03:33:18 PM
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