

**One Year Post-Exclusivity Adverse  
Event Review:  
Tolterodine**

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# Background Drug Information

- **Drugs:** Detrol<sup>®</sup> and Detrol<sup>®</sup> LA
  - Tolterodine tartrate is the active ingredient in both drugs.
- **Therapeutic category:** Muscarinic receptor antagonist
- **Sponsor:** Pfizer
- **Indication:** Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency
- **Original Market Approval:** March 25, 1998 for Detrol<sup>®</sup> and December 22, 2000 for Detrol LA<sup>®</sup>
- **Pediatric Exclusivity granted:** January 5, 2004

# Drug Use Trends in Children

- Almost all pediatric (1-16 years) use for both drugs was in out-patient setting; estimated pediatric prescriptions during 2004: Detrol<sup>®</sup> 14,448, Detrol LA<sup>®</sup> 53,976 <sup>1</sup>
- 1.4% of all Detrol<sup>®</sup> and 0.8% of all Detrol LA<sup>®</sup> claims during 2/04-1/05 were for children. <sup>1</sup>
- Detrol<sup>®</sup> usage decreased by 33% and Detrol LA<sup>®</sup> usage increased by 50% in children from 2/02-1/03 period to 2/04-1/05 period. Detrol LA<sup>®</sup> prescription claims were 4 times greater than Detrol<sup>®</sup> during post-exclusivity period. <sup>1</sup>
- Pediatric hospital discharges accounted for  $\leq 0.2\%$  of all discharges in which a tolterodine product was mentioned from 7/03-6/04. <sup>2</sup>

<sup>1</sup>Caremark Dimension RX™, Feb 2002 - Jan 2005, Data extracted Mar 2005

<sup>2</sup>Premier Inc., Jul 2003 - Jun 2004, Data extracted Apr 2005

# Pediatric Exclusivity Studies

- Three pharmacokinetic (PK), pharmacodynamic (PD) [urodynamic] and safety studies
- One clinical efficacy, PK and safety study in patients with overactive bladder

# PK, PD and Safety Studies in Neurologically Impaired Patients

- **Three 12-week, open-label, dose escalation studies:**
  - 1 month-4 year olds (n=19) received 0.03, 0.06, 0.12 mg/kg/d Detrol<sup>®</sup> immediate-release syrup
  - 5-10 year olds (n=15) received 0.03, 0.06, 0.12 mg/kg/d Detrol<sup>®</sup> immediate-release syrup
  - 11-15 year olds (n=11) received 2, 4, 6 mg/day Detrol LA<sup>®</sup> capsules
    - Of patients in all studies, 78% had myelomeningocele; others had spinal cord injury or anomaly
- Urodynamic data inconsistent within and across trials
- Lack of dose-response trends across studies

# **Phase 3 Efficacy, PK and Safety Studies in Neurologically Intact Patients**

- **Two multi-center randomized, placebo-controlled, blinded studies of tolterodine extended –release capsules, 2 mg/day for 12 weeks for the indication: treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency**
  - **5-10 year olds, 235 treated with drug, 107 with placebo**
  - **5-10 year olds, 251 treated with drug, 117 with placebo**
  - **Detrol LA<sup>®</sup> dose was chosen after comparison of the PK of tolterodine and DD01 (the active metabolite) in children, 5 to 10 years, with adults**
- **Primary efficacy endpoints for both studies were change from baseline in number of weekly incontinence episodes during waking hours after 12 weeks of treatment**
- **No significant difference in outcome between Detrol LA<sup>®</sup> and placebo**
- **Label states that efficacy in children not demonstrated**

# **Integrated Review of Safety from Pediatric Studies**

- **Database from pediatric exclusivity studies and other pediatric studies conducted by Sponsor**
  - **917 unique patients exposed to tolterodine**
  - **No deaths**
  - **24 Serious Adverse Events (SAEs) in 20 patients including 4 lower UTIs; 4 with pyelonephritis (one in placebo group)**
  - **18 patients manifested aggressive and/or abnormal behavior, categorized as non-serious AEs**
  - **Excess of UTIs and abnormal behavior in tolterodine- treated patients compared to placebo are included in Detrol LA<sup>®</sup> label**

# Summary of Labeling Changes Resulting from Exclusivity Studies

- **Detrol LA<sup>®</sup>:**
  - Efficacy not demonstrated
  - PK: Dose-plasma concentration relationship linear; parent/metabolite ratios differed according to enzyme metabolizer status
  - Percentage of UTIs in 5-10 year olds higher with Detrol LA<sup>®</sup> (6.6%) compared to placebo (4.5%)
  - Aggressive, abnormal and hyperactive behavior and attention disorders higher with Detrol LA<sup>®</sup> (2.9%) compared with placebo (0.9%)

**Pediatric Adverse Events for Detrol<sup>®</sup> and  
Detrol LA<sup>®</sup>:  
One-Year Post-Exclusivity Period**

- **No AE reports received**

# **Pediatric Adverse Event Reports after Marketing Approval for Detrol<sup>®</sup> (03/25/1998) and Detrol LA<sup>®</sup> (12/22/2000) through 02/05/2005**

- **31 reports\* (25 U.S.);  
29 unduplicated reports**
  - **25 Detrol<sup>®</sup>, 4 Detrol LA<sup>®</sup>**
  - **Positive de-challenge in 15 patients; positive re-challenge in one patient**

# Categories of Pediatric Adverse Event Reports for Detrol<sup>®</sup> and Detrol LA<sup>®</sup> (N=29)

- Anti-cholinergic events (9 reports): confusion, lethargy, urine retention, overheating, constipation, flushing, dry mouth, blurry vision
- CNS stimulation (8 reports): aggression\*, hyperactivity\*, irritability, insomnia
- Anti-cholinergic plus CNS stimulation (2 reports)
- UTI (2 reports)
- Medication error (3 reports)
- Other (5 reports)

\* Unlabeled in Detrol<sup>®</sup> label

Underlined = Unlabeled events in Detrol<sup>®</sup> and Detrol LA<sup>®</sup> labels

# **Pediatric Adverse Event Reports for Detrol<sup>®</sup> and Detrol LA<sup>®</sup>: Marketing Approval through 02/05/2005**

- **In 18 reports, the outcome was reported as serious.**
  - **Upon careful review of the 18 reports, there were:**
    - **0 deaths**
    - **5 hospitalizations**
    - **1 disability**
    - **2 older than 16 years (85 and 16.5 years old)**
    - **10 non-serious**

# **Pediatric Adverse Event Reports for Detrol<sup>®</sup> and Detrol LA<sup>®</sup> with Serious Outcomes since Market Approval**

- **6 reports with serious outcomes:**
  - **Hospitalizations**
    - **One patient with breathing difficulty, nocturnal laryngitis and cough; resolved after tolterodine was discontinued; possibly related to drug;**
    - **One patient with transient blindness; event continued after drug was discontinued**
    - **One patient developed heart block, dizziness and chest pain; also on azathioprine; heart block resolved upon stopping tolterodine**
    - **One patient with exfoliative skin rash; positive culture for HSV**
    - **One patient developed convulsions**
  - **Disability**
    - **Hyperactivity**

# **Request for Labeling Revision Issued for Detrol<sup>®</sup>**

- **Sponsor has been requested by FDA to incorporate safety information that already exists in Detrol LA<sup>®</sup> label into Detrol<sup>®</sup> label in Pediatric Use section**
  - **Increased incidence of UTIs and abnormal behavior in tolterodine-treated patients compared with placebo**
  - **Pediatric efficacy not demonstrated**

# Conclusion

- **This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.**
- **FDA recommends routine monitoring of AEs for this drug in all populations.**
- **Does the Advisory Committee concur?**

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