

Memorandum

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Food and Drug Administration
Center for Drug Evaluation and Research**

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SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data
Tolterodine: Detrol[®] tablets (NDA 20-771) and Detrol[®]LA (21-241) tablets

****This document contains proprietary data from IMS Health and Caremark which cannot be shared outside of FDA without clearance from IMS Health and Caremark obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for tolterodine products, Detrol[®] and Detrol[®] LA, in the pediatric population (ages 1-16 years), with a primary focus on patterns of use one-year before and one-year following the granting of Pediatric Exclusivity on January 5, 2004. Proprietary drug use databases licensed by the Agency were used to determine the various retail and non-retail channels of distribution. Although the majority of product usage occurs in the outpatient setting, we included both the inpatient and outpatient settings in our review. Outpatient use was measured by two IMS Health Audits, the National Prescription Audit *Plus*[™] (NPA *Plus*[™]) and the National Disease and Therapeutic Index[™] (NDTI[™]), along with prescription claims for a 36-month period of time from Caremark (Dimension RX[™]). Outpatient drug utilization patterns were examined for the 3-year period from February 1, 2002 to January 21, 2005. Inpatient use was examined using Premier's large sample of acute care, short stay hospitals, as well as Premier's subset of pediatric hospitals. Inpatient use patterns were examined for the 6 months before and after the granting of pediatric exclusivity, a 1-year period from July 1, 2003 to June 30, 2004.

Retail channels were the largest purchasers of Detrol[®] and Detrol[®] LA, representing over 80% of the total sales in each of the three one-year periods in this analysis. In terms of dispensed prescriptions in the outpatient setting, Detrol[®] and Detrol[®] LA combined held approximately 52-53% of the selected market share of oral anticholinergics and antispasmodics used for urinary incontinence during the time period analyzed. During this time period, Detrol[®] LA was the most commonly dispensed product, holding approximately 45% of the selected market share during the most recent 12-month period, February 2004 – January 2005. Detrol[®] was the fourth most commonly dispensed product in this market, accounting for approximately 7% of the selected market share during February 2004 – January 2005.

Internal medicine and family practice were the most frequent specialties that prescribed Detrol[®] and Detrol[®] LA from February 2002- January 2005. Pediatricians ranked 20th in prescribing both Detrol[®] and Detrol[®] LA, accounting for no more than 0.5% of dispensed Detrol[®] or 0.3% of Detrol[®] LA prescriptions in each of the three years surveyed in this analysis. The proportion of provider specialties prescribing Detrol[®] and Detrol[®] LA in the outpatient retail pharmacy settings showed no substantial change during the 36-month study period.

Pediatric participants age 1-16 years in the Caremark system accounted for no more than 1.4% of claims for Detrol[®] and 0.8% of claims for Detrol[®] LA from February 2002 to January 2005. Based on these data, we estimate that 14,448 prescriptions of Detrol[®] and 53,976 prescriptions of Detrol[®] LA have been dispensed for pediatric participants aged 1-16 years in the U.S. during 2004 from retail pharmacies.

The most common diagnosis associated with a mention of Detrol[®] and Detrol[®] LA for adults in office-based physician patient encounters was “incontinence of urine” (ICD-9 code 788.3) followed by “other functional disorders of bladder “ (ICD-9 code 596.5), which accounted for 36% -38% and 25-26% of mentions, respectively, during the post-exclusivity period (February 2004 - January 2005). Diagnoses in pediatric patients accounted for no more than 3.3% of all mentions associated with Detrol[®] from February 2002- January 2005, while diagnoses in pediatric patients accounted for 0.6% of all mentions associated with Detrol[®] LA. “Incontinence of urine” (ICD-9 code 788.3) was the most common use mentioned for both products in pediatric patients. Other diagnoses mentioned during the 36-month time period include “other functional disorders of bladder” (ICD-9 code 596.5), “post-op surgical exam” (V67.0), and “cauda equina syndrome” (344.6).

There were 17,634 actual discharges in which tolterodine was billed in Premier’s 450 acute short-stay hospitals from January to June 2004. Pediatric discharges accounted for no more than 0.2% of discharges in which a tolterodine product was mentioned from June 2003 to July 2004 in these hospitals. In a subset of 37 Premier Network pediatric hospitals and care centers, only 11 pediatric discharges in which tolterodine was billed occurred during July 2003 through December 2003, and 7 discharges in which tolterodine was billed occurred during January 2004 through June 2004. Of those, the majority of discharges were associated with pediatric patients aged 2-11 years during both 6-month periods.

In summary, Detrol[®] usage has been decreasing over the past three years in both populations while Detrol[®] LA use has been increasing. Pediatric prescriptions claims account for 1.4% of Detrol[®] prescriptions and 0.8% of Detrol[®] LA prescriptions. During February 2004 – January

2005, the number of prescriptions for Detrol[®] LA was almost four times the number of prescriptions for Detrol[®] for the pediatric population.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Detrol[®] (NDA 20-771) and Detrol[®] LA (NDA 21-228) are anticholinergic agents. Detrol[®] is available as a 1 mg and 2 mg tablet for oral use. Detrol[®] LA is available as a 2 mg and 4 mg capsule for oral use.

Detrol[®] was approved on March 25, 1998, and Detrol[®] LA on December 22, 2000, for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. According to the labeling, the safety and efficacy of Detrol[®] has not been established in pediatric patients. The labeling of Detrol[®] LA states that efficacy in the pediatric population has not been established.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Detrol[®] and Detrol[®] LA on January 5, 2004.

This review describes outpatient drug usage of Detrol[®] and Detrol[®] LA Tablets in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

A. Defining settings of use

To obtain a comprehensive overview of trends, Detrol[®], Detrol[®] LA, and all oxybutynin branded and generic products were examined. These agents were selected to define this market because they represent oral antispasmodics and anticholinergics used to treat lower urinary tract dysfunction. IMS Health, IMS National Sales Perspectives[™] data were first used to determine the setting in which the product was sold. A description of this data source appears below:

IMS HEALTH, IMS NATIONAL SALES PERSPECTIVES[™]

IMS Health National Sales Perspectives[™] measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug

stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

For this analysis, the sales trend for Detrol[®] and Detrol[®] LA was examined from February 1, 2002 – January 31, 2005 inclusive.

Sales of Detrol[®] and Detrol[®] LA by number of tablets sold from the manufacturer to various retail and non-retail channels of distribution were analyzed (Table 1). These products are distributed largely to the outpatient setting, although inpatient distribution was as high as 17%. Therefore, this review focuses on both outpatient and inpatient utilization.

Table 1. Total Number of Tablets and Capsules (in thousands) of Tolterodine (Detrol[®] and Detrol[®] LA) Sold to U.S. Distribution Channels During February 2002 – January 2005

	February 2002 – January 2003		February 2003 – January 2004		February 2004 – January 2005		Percent Change 2002- 2005
	N (000)	%	N (000)	%	N (000)	%	
Tolterodine§	339,373	(100)	338,367	(100)	346,903	(100)	(2)
*Retail	294,082	(87)	284,494	(84)	287,740	(83)	(-2)
**Non-Retail	45,294	(13)	53,872	(16)	59,161	(17)	(31)

§Detrol[®] and Detrol[®] LA

*Retail includes chain, independent, mail order, long term care and food store pharmacies

**Non-retail includes Non-federal hospitals, federal facilities, clinics, HMOs, home health care, prisons, universities, and other

IMS Health, IMS National Sales Perspectives™ Combined, February 2002 to January 2005, Data Extracted 03-2005
(Original files: 0503desp.xls)

DATA SOURCES

Outpatient and inpatient drug use patterns of Detrol[®] and Detrol[®] LA in the pediatric population were compared to the adult population two years before and one year after the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis and are described below in detail.

Outpatient:

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database

account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis covers all prescriptions dispensed from February 1, 2002 – January 31, 2005 inclusive.

CAREMARK™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 75 million participant lives, and processing over 450 million prescription claims annually. FDA has access to Caremark's database of paid claims for prescriptions filled in approximately 55,000 pharmacies across the country. Patients whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark's data includes participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in Caremark to all persons receiving dispensed prescriptions in the U.S., however, is not known.

For this analysis, prescription claims for participants in the Caremark system were examined from February 1, 2002 – January 31, 2005 inclusive.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a drug use does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of Detrol® and Detrol® LA during office-based physician visits during the time period from February 1, 2002 – January 31, 2005 inclusive.

Inpatient:

PREMIER™

Premier maintains a large hospital drug utilization and financial database. The database contains information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly, one out of every seven inpatient discharges in the U.S. is represented in Premier's database. Data are available from January 2000 through the present, but have a lag time of approximately six months. Premier's primary mission is to assist health care institutions improve clinical and operating performance in three strategic areas: group purchasing, supply chain and healthcare informatics. To that end, Premier developed this database in part to analyze utilization of resources to improve clinical efficiency.

The hospitals that contribute information to the database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. Based upon these analyses, we believe that most estimates of national inpatient drug use based on Premier data appear to be reasonable, but strongly recommend making this determination on a drug-specific basis. For tolterodine, we did not use projected estimates, given the very competitive marketplace for these products getting on a hospital formulary. Therefore, we cannot be sure that Premier purchasing agreements are truly representative of hospitals nationwide. Rather the Premier data provide a glimpse of practice in approximately 450 acute, short-stay hospitals.

For this analysis, the total number of distinct discharges within Premier hospitals which included claims for tolterodine was examined in two six-month increments for the time period from July 1, 2003 to June 30, 2004, inclusive.

PREMIER PEDIATRIC™

Premier's pediatric database represents a subset of information from 37 pediatric hospitals. In addition, Premier maintains data on all pediatric discharges from the larger sample of approximately 450 acute care facilities. Overall, the pediatric population in Premier's pediatric database includes greater than 3 million inpatient records. Data are available from January 2000 through the present, but have a lag time of approximately six months.

For this analysis, the total number of distinct discharges associated with tolterodine use within these 37 tertiary care pediatric hospitals were examined from July 1, 2003 to June 30, 2004, inclusive.

RESULTS

I. Dispensed Prescriptions

During the time period reviewed, dispensed prescriptions for the selected agents increased 4% from 14.5 million prescriptions during the pre-exclusivity period (February 2003 – January 2004) to approximately 15.1 million prescriptions during the post-exclusivity period (February 2004 to January 2005) (Table 2).

Detrol[®] and Detrol[®] LA combined held approximately 52-53% of the market share during the time period analyzed (Table 2). Detrol[®] LA led the market during February 2002 to January 2003 with 37% of the annual market share. By February 2004 to January 2005 it rose to hold 45% of the market share, which represented a 29% increase from 5.2 million prescriptions to 6.7 million prescriptions. From February 2002 to January 2003, Detrol[®] held approximately 16% of the selected market. By February 2004 to January 2005, Detrol[®]'s market share dropped to 7% of the selected market. This represented a 53% relative decline in prescriptions dispensed. During the post exclusivity period (February 2004 to January 2005), there was a 27% decline in dispensed prescriptions for Detrol[®] from approximately 1.4 million to 1.0 million prescriptions dispensed. A 35% decline occurred during the second year of pre-exclusivity (February 2003-January 2004), relative to the first year (February 2002-January 2003).

Table 2: Total Number of Prescriptions Dispensed (in thousands) in Retail Pharmacies Nationwide for Selected Market for the period of February 2002 – January 2005

	February 2002 – January 2003		February 2003 – January 2004		February 2004 – January 2005	
	N (000)*	(%)	N (000)*	(%)	N (000)*	(%)
Total Selected Market	14,071	(100)	14,482	(100)	15,087	(100)
Detrol[®] LA	5,224	(37)	6,083	(42)	6,747	(45)
Ditropan XL	3,928	(28)	4,170	(29)	4,028	(27)
Oxybutynin (generic) (31)	2,543	(18)	2,464	(17)	2,534	(17)
Detrol[®]	2,191	(16)	1,431	(10)	1,032	(7)
Ditropan	38	(0.3)	25	(0.2)	17	(0.1)
Oxytrol	-----	-----	185	(1)	548	(4)
Other (6)	149	(1)	122	(1)	178	(1)

IMS Health, NPA Plus[™] data extracted 03-2005 (Original file: 0503deus.xls)

*Numbers may not sum exactly due to rounding error.

Prescriber Specialty

Internal medicine and family practice were the most frequent prescribers of Detrol[®] and Detrol[®] LA from February 2002- January 2005 (Table 3). In the period February 2004-January 2005, internal medicine specialists were responsible for a combined total of over 1.4 million (25%) dispensed prescriptions of Detrol[®] and Detrol[®] LA, followed by family practitioners with 1.2 million (21%) (derived from data in Table 3). Urologists ranked third in prescribing, accounting for 6% of dispensed prescriptions for Detrol[®] and 21% of dispensed prescriptions for Detrol[®] LA, for a combined total of approximately 1.1 million (19%) of dispensed prescriptions. Pediatricians ranked 20th in prescribing both Detrol[®] and Detrol[®] LA, accounting for no more than 0.5% of dispensed Detrol[®] or 0.3% of Detrol[®] LA prescriptions in each of the three years surveyed in this analysis. The proportion of provider specialties prescribing Detrol[®] and Detrol[®] LA in the outpatient retail pharmacy settings showed no substantial change during the 36-month study period.

Table 3: Total Number of Prescriptions Dispensed (in thousands) for Detrol® and Detrol® LA Nationwide by Physician Specialty from February 2002 – January 2005*

Prescriber specialty	February 2002 – January 2003		February 2003 – January 2004		February 2004 – January 2005	
	N (000)**	(%)	N (000)**	(%)	N (000)**	(%)
Total	5,772	(100)	5,742	(100)	5,824	(100)
Detrol®	1,648	(100)	1,064	(100)	766	(100)
1 st Internal Medicine	471	(54)	318	(52)	233	(53)
2 nd Family Practice	368	(16)	248	(15)	185	(13)
3 rd Urology	222	(4)	123	(5)	79	(6)
4 th Osteopathic Medicine	128	(6)	82	(6)	59	(6)
5 th Obstetrics/Gynecology	118	(6)	63	(6)	39	(6)
20 th Pediatrics	7	(0.4)	5	(0.4)	4	(0.5)
Other Practices (66)	328	(14)	226	(12)	165	(7)
Detrol® LA	4,125	(100)	4,677	(100)	5,058	(100)
1 st Internal Medicine	889	(22)	1,088	(23)	1,211	(24)
2 nd Family Practice	745	(18)	927	(20)	1,046	(21)
3 rd Urology	1,050	(25)	1,030	(22)	1,039	(21)
4 th Obstetrics/Gynecology	536	(13)	557	(12)	551	(11)
5 th Osteopathic Medicine	309	(7)	365	(8)	407	(8)
20 th Pediatrics	13	(0.3)	15	(0.3)	17	(0.3)
Other Practices (67)	580	(14)	693	(15)	783	(15)

IMS Health NPA Plus™, February 2002- January 2005, Data extracted 03-2005, (original file: 0503demd.xls)

*excludes Mail Order and Long Term Care

**Numbers may not sum exactly due to rounding error.

II. Patient Demographics

Among a large, insured population whose outpatient pharmacy benefits are managed by Caremark, pediatric participants age 1-16 years accounted for no more than 1.4% of claims for Detrol® and 0.8% of claims for Detrol® LA from February 2002 to January 2005 (Table 4).

The total number of claims for Detrol® decreased from 260,915 claims from February 2002 to January 2003 to 114,565 claims from February 2004 to January 2005, representing a 56% decline in prescriptions dispensed. This is consistent with dispensed prescription data from IMS Health. Although the number of claims decreased in both the adult and pediatric populations, the proportion of pediatric claims increased slightly from 0.9% to 1.4% during this time period. Total prescription claims for Detrol® LA increased from 678,362 claims in January 2002 to February 2003 to 811,066 claims in 2004, which represented a 20% increase in claims. The proportion of pediatric claims also increased slightly from 0.6% in February 2002 to January 2003 to 0.8% in February 2004 to January 2005.

Table 4: Total Number (Absolute) of Paid Prescription Claims by Age for Detrol® and Detrol® LA for Participants From Caremark Dimension Rx™ Pharmacy Benefit Manager Database.

	Feb 2002-Jan 2003		Feb 2003-Jan 2004		Feb 2004-Jan 2005	
	N	(%)	N	(%)	N	(%)
Detrol® (Total)	260,915	(100)	162,842	(100)	114,565	(100)
Peds (1-16 yrs)	2,419	(0.9)	2,016	(1.2)	1,628	(1.4)
Adults (17+ yrs)	258,496	(99.1)	160,826	(98.7)	112,937	(98.6)
Detrol® LA (Total)	678,362	(100)	772,647	(100)	811,066	(100)
Peds (1-16 yrs)	4,347	(0.6)	5,590	(0.7)	6,530	(0.8)
Adults (17+ yrs)	674,015	(99.4)	767,057	(99.3)	804,536	(99.2)

Caremark Dimension Rx™: Extracted March 23, 2005.

Since IMS Health, NPA *Plus*™ does not include demographic information on participants for the entire time period of interest, proportions were applied for demographic subgroups from Caremark’s Dimension Rx™ to IMS Health, NPA *Plus*™ data to estimate the number of prescriptions dispensed nationwide to children for Detrol® and Detrol® LA (Table 5). Using this approach, approximately 14,448 prescriptions of Detrol® and 53,976 prescriptions of Detrol® LA are estimated to have been dispensed for pediatric participants aged 1-16 years in the U.S. during 2004 from retail pharmacies. The number of prescriptions for Detrol® LA was almost four times the number of prescriptions for Detrol® for the pediatric population.

Table 5: Estimated Nationwide Prescriptions Dispensed for Pediatric Age Group (1-16) During February 2004 to January 2005

	Total Number of Prescriptions* Dispensed for All Age Groups (from Table 2)	% Pediatric Claims** (Age 1-16yrs) (from Table 4)	Estimated Number of Prescriptions Dispensed to Pediatric Population (Age 1-16 yrs)
Detrol®	1,032,000	1.4%	14,448
Detrol® LA	6,747,000	0.8%	53,976

* IMS Health, NPA *Plus*™, February 2004 to January 2005, data extracted 03-2005 (Original file: 0503deus.xls)

** Caremark Dimension Rx™: Extracted March 23, 2005.

III. Indications for Use

The most common diagnosis associated with a mention of Detrol® and Detrol® LA for adults in office-based physician patient encounters was “incontinence of urine” (ICD-9 code 788.3) followed by “other functional disorders of bladder “ (ICD-9 code 596.5), which accounted for 36% -38% and 25-26% of mentions, respectively, during the post-exclusivity period (February 2004 - January 2005) (Table 6). Pediatric diagnoses accounted for no more than 3.3% of all mentions associated with Detrol® from February 2002- January 2005, while pediatric diagnoses accounted for 0.6% of all mentions associated with Detrol® LA. During the time period surveyed, “incontinence of urine” (ICD-9 code 788.3) was the most common use mentioned for both products. Other diagnoses mentioned during the 36-month time period include “other functional disorders of bladder” (ICD-9 code 596.5), “post-op surgical exam” (V67.0), and “cauda equina syndrome” (344.6).

Table 6: Top Diagnoses Associated with Projected Mentions of Detrol® and Detrol® LA for Pediatric and Adult Patients During January 2002 - December 2004

ICD-9 Code	Feb 2002-Jan 2003		Feb 2003-Jan 2004		Feb 2004-Jan 2005	
	N	(%)	N	(%)	N	(%)
Detrol® Total Mentions	287,460	(100.0)	157,193	(100.0)	115,240	(100.0)
Patient age 17+ Years	277,904	(96.6)	153,677	(97.7)	115,240	(100.0)
788.3 Incontinence of Urine	98,993	(36)	54,832	(36)	41,748	(36)
596.5 Bladder Function Dis Oth	39,093	(14)	22,549	(15)	29,709	(26)
596.8 Bladder Disorders Oth	29,201	(11)	-----	-----	13,429	(12)
788.4 Freq of Urination & Polyuria	28,012	(10)	14,507	(9)	9,028	(7)
625.6 Stress Incontinence	6,772	(2)	12,027	(8)	2,207	(2)
799.9 Unk & Unspec Cause Oth	8,807	(3)	15,027	(10)	1,850	(2)
Other Diagnoses (17)	67,026	(24)	34,735	(23)	6,154	(5)
Patient age 1-16 Years	9,556	(3.3)	3,516	(2.2)	-----	-----
V67.0 Post Op Surgical Exam	1,661	(17)	-----	-----	-----	-----
788.3 Incontinence of Urine	7,895	(83)	3,516	(100)	-----	-----
Detrol® LA Total Mentions	1,569,834	(100.0)	1,669,444	(100.0)	1,485,397	(100.0)
Patient age 17+ Years	1,560,040	(99.4)	1,647,204	(98.6)	1,476,145	(99.3)
788.3 Incontinence of Urine	601,280	(39)	663,231	(40)	553,912	(38)
596.5 Bladder Function Dis Oth	320,499	(21)	350,181	(21)	366,521	(25)
788.4 Freq of Urination & Polyuria	174,036	(11)	164,127	(10)	86,086	(6)
625.6 Stress Incontinence	152,952	(10)	129,889	(8)	103,984	(7)
596.8 Bladder Disorders Oth	43,895	(3)	64,387	(4)	45,659	(3)
Other Diagnoses (36)	267,378	(17)	275,389	(17)	319,983	(22)
Patient age 1-16 Years	9,794	(0.6)	22,240	(1.3)	9,252	(0.6)
788.3 Incontinence of Urine	5,922	(60)	5,183	(23)	7,363	(80)
344.6 Cauda Equina Syndrome	1,936	(20)	5,110	(23)	-----	-----
596.5 Bladder Function Dis Oth	1,936	(20)	5,651	(25)	1,889	(20)

IMS National Disease and Therapeutic Index™ CD-ROM, NDTI 6yr. January 1999-December 2004. Data extracted 03-22-2005 (File 0503detrolicd9.xls)

IV. Inpatient Usage

There were 17,634 actual discharges in which tolterodine was billed in Premier's 450 acute short-stay hospitals from January to June 2004 (Table 7). This represented a 4% decrease from 18,375 actual discharges from July-December 2003. Pediatric discharges accounted for no more than 0.2% of total discharges from July 2003 to June 2004. On the other hand, the use of oxybutynin products in the pediatric population was 14-21 times higher than the combined use of Detrol® and Detrol® LA during these 6-month time intervals.

Table 7: Total Number (Absolute) of Discharges in which Detrol[®], Detrol[®] LA, and Oxybutynin were billed from Premier Inpatient Database.

	Number of Discharges			
	July- December 2003		January- June 2004	
	N	(%)	N	(%)
Detrol[®] and Detrol[®] LA (Total)	18,375	(100)	17,634	(100)
Peds (0-16 yrs)	25	(0.1)	30	(0.2)
Adults (17+ yrs)	18,350	(99.9)	17,604	(99.8)
Oxybutynin (Total)	22,207	(100)	19,927	(100)
Peds (0-16 yrs)	526	(2.4)	404	(2.1)
Adults (17+ yrs)	21,681	(97.6)	19,523	(97.9)

Premier Inc: Extracted April 1, 2005

Since tolterodine billing data from Premier’s subset of pediatric hospitals was so low, Detrol[®] and Detrol[®] LA data were combined for the subsequent analyses. Detrol[®] and Detrol[®] LA usage data from a subset of 37 Premier Network pediatric hospitals and care centers yielded only 11 pediatric discharges during July 2003 through December 2003, and 7 discharges during January 2004 through June 2004. Of those, the majority of discharges were associated with pediatric patients aged 2-11 years during both 6-month periods.

The use of oxybutynin products was more prevalent in the 37 pediatric hospitals. There were a total of 380 discharges associated with use of all oxybutynin products from July 2003 to December 2003, and 280 discharges during January 2004 through June 2004. As with Detrol[®] and Detrol[®] LA, the majority of use was associated with pediatric patients aged 2-11 years.

Table 8: Total Number (Absolute) of Discharges for Patients Aged 0-16 Years in which Detrol[®], Detrol[®] LA, and Oxybutynin were billed from Premier’s Pediatric Hospital Inpatient Database.

	Number of Discharges			
	July- December 2003		January- June 2004	
	N	(%)	N	(%)
Detrol[®] and Detrol[®] LA (Total)	11	(100)	7	(100)
Age 0-1	-----	-----	-----	-----
Age 2-11	6	(55)	6	(86)
Age 12-16	5	(45)	1	(14)
Oxybutynin (Total)	380	(100)	280	(100)
Age 0-1	51	(13)	31	(11)
Age 2-11	252	(66)	195	(70)
Age 12-16	77	(20)	54	(19)

Premier Inc: Extracted April 1, 2005

LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus[™] data provide an estimate of the total number of prescriptions

dispensed in the U.S. However, NPA Plus™ does not include complete demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels. This may be significant, as mail order and long-term care prescriptions sales account for approximately 30% of total sales for both Detrol® and Detrol® LA combined.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not common in the pediatric population, as in the case of Detrol® and Detrol® LA.

Caremark data cannot be projected to provide national estimates, but its large sample size can be helpful for replicating demographic findings in IMS Health's NDTI™, where sample sizes are often small. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations based on the proportion dispensed to pediatric participants in the Caremark system are dependent upon the assumption that these patterns are similar across populations with and without prescription drug coverage. The accuracy of this assumption is not known at this time. In addition, reliable information for participants less than the age of 1 year is not available from this data source.

The inpatient data from Premier, while providing a helpful view of the use of tolterodine products in the hospital setting, cannot be projected to provide nationwide estimates of the use of this product in children hospitalized throughout the U.S. Although the use of tolterodine products within the large sample of general hospitals (~450 hospitals) and the smaller sample of children's hospitals and care centers (37 hospitals and centers) is informative, an appropriate method for projecting these estimates is not yet available.

CONCLUSION

Retail channels were the largest purchasers of Detrol® and Detrol® LA, representing over 80% of the total sales in each of the three one-year periods in this analysis. In terms of dispensed prescriptions in the outpatient setting, Detrol® and Detrol® LA combined held approximately 52-53% of the market share during the time period analyzed. During this time period, Detrol® LA was the most commonly dispensed product, holding approximately 45% of the selected market share during the most recent 12-month period, February 2004 – January 2005. Detrol® was the fourth most commonly dispensed product in this market, accounting for approximately 7% of the selected market share during February 2004 – January 2005.

Internal medicine and family practice were the most frequent specialties that prescribed Detrol® and Detrol® LA from February 2002- January 2005. Pediatricians ranked 20th in prescribing both Detrol® and Detrol® LA, accounting for no more than 0.5% of dispensed Detrol® or 0.3% of Detrol® LA prescriptions in each of the three years surveyed in this analysis. The proportion of provider specialties prescribing Detrol® and Detrol® LA in the outpatient retail pharmacy settings showed no substantial change during the 36-month study period.

Pediatric participants age 1-16 years in the Caremark system accounted for no more than 1.4% of claims for Detrol[®] and 0.8% of claims for Detrol[®] LA from February 2002 to January 2005. Based on these data, we estimate that 14,448 prescriptions of Detrol[®] and 53,976 prescriptions of Detrol[®] LA have been dispensed for pediatric participants aged 1-16 years in the U.S. during 2004 from retail pharmacies.

The most common diagnosis associated with a mention of Detrol[®] and Detrol[®] LA for adults in office-based physician patient encounters was “incontinence of urine” (ICD-9 code 788.3) followed by “other functional disorders of bladder “ (ICD-9 code 596.5), which accounted for 36% -38% and 25-26% of mentions, respectively, during the post-exclusivity period (February 2004 - January 2005). Pediatric diagnoses accounted for no more than 3.3% of all mentions associated with Detrol[®] from February 2002- January 2005, while pediatric diagnoses accounted for 0.6% of all mentions associated with Detrol[®] LA. “Incontinence of urine” (ICD-9 code 788.3) was the most common use mentioned for both products in pediatric patients. Other diagnoses mentioned during the 36-month time period include “other functional disorders of bladder” (ICD-9 code 596.5), “post-op surgical exam” (V67.0), and “cauda equina syndrome” (344.6).

There were 17,634 actual discharges in which tolterodine was billed in Premier’s 450 acute short-stay hospitals from January to July 2004. Pediatric discharges accounted for no more than 0.2% of total discharges from July 2003 to July 2004 in these hospitals. In a subset of 37 Premier Network pediatric hospitals and care centers, only 11 pediatric discharges were billed during July 2003 through December 2003, and 7 discharges were billed during January 2004 through June 2004. Of those, the majority of discharges were associated with pediatric patients aged 2-11 years during both 6-month periods.

In summary, Detrol[®] usage has been decreasing over the past three years in both populations while Detrol[®] LA use has been increasing. Pediatric prescriptions claims account for 1.4% of Detrol[®] prescriptions and 0.8% of Detrol[®] LA prescriptions. During February 2004 – January 2005, the number of prescriptions for Detrol[®] LA was almost four times the number of prescriptions for Detrol[®] for the pediatric population.

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