

**MEMORANDUM**

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

**PID#:** D060560

**DATE:** September 14, 2006

**TO:** Lisa L. Mathis, M.D., Associate Director  
Pediatric and Maternal Health Staff (PMHS)  
Office of New Drugs (OND), CDER  
and  
M. Dianne Murphy, M.D., Director  
Office of Pediatric Therapeutics (OPT), OC

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

**THROUGH:** Rosemary Johann-Liang, M.D., Deputy Director  
for  
Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation

**SUBJECT:** Post-Pediatric Exclusivity Postmarketing Adverse Event Review:  
**UPDATE for Fall 2006 Pediatric Advisory Committee meeting**  
Drug: Oxybutynin  
Pediatric Exclusivity Approval Date: February 8, 2002

**1. Executive Summary**

In July 2006, the Office of Pediatric Therapeutics requested the Division of Drug Risk Evaluation (DDRE) complete an updated review of all pediatric AERS cases in association with oxybutynin received since pediatric exclusivity was granted on February 8, 2002.

Since approval in 1975 (see Table 1) AERS has received a total of 1639 reports in association with oxybutynin (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 7% of the total number of reports (114/1639).

A previous review of pediatric reports was completed in May 2003 (attached – see appendix). The consult focused on 6 pediatric AERS reports (representing 5 unduplicated cases) that were received in the first 13 months following the approval of

pediatric exclusivity (February 8, 2002 - March 19, 2003). The consult concluded that the events could not be attributed solely to oxybutynin due to confounders such as other co-suspect drugs, overdosing, or underlying conditions. The Office of Pediatric Therapeutics considered the reports too few for meaningful analysis and requested adverse event monitoring continue beyond the first 13 months of pediatric exclusivity.

Since the initial pediatric exclusivity consult AERS has received another 14 pediatric reports (see Table 2) for a total crude count of 20 reports (representing 15 unduplicated cases) since pediatric exclusivity was granted (55 month period: February 8, 2002 – August 30, 2006). Most of the patients were 6 to 11 years of age and the most common indication was nocturnal enuresis (an unapproved indication). Oxybutynin is not recommended for children under the age of five years however 5 of the 15 patients were younger than five years. No deaths were reported. Thirteen of the 15 unduplicated cases were serious.

Seven of the 13 serious cases appeared to be related to other drugs/underlying conditions or did not contain enough information to attribute a direct relationship to oxybutynin. One of the 6 remaining serious cases reported an extrapyramidal reaction (an unlabeled event) in a 10 year old boy; however this information alone is not enough to make an association between oxybutynin and extrapyramidal reactions.

The 5 remaining serious cases reported labeled events that may be due to anticholinergic effects of oxybutynin, particularly anticholinergic CNS excitation (hallucinations, irritability, insomnia). Overall there are a disproportionate number of CNS excitation reports since approval in pediatric patients versus adult patients. Consideration should be given for adding text to the label that emphasizes the potential for pediatric patients to develop CNS excitation following oxybutynin treatment.

## **2. Products, Indications, Pediatric Labeling, and Pediatric Filing History**

Oxybutynin (Ditropan® tablets, syrup, extended release tablets and Oxytrol™ transdermal patch) were first approved in July 1975, November 1979, December 1998, and February 2003 respectively, for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).

The labeling for the immediate release tablets and syrup indicates that “the safety and efficacy of Ditropan administration have been demonstrated for pediatric patients 5 years of age and older (see Dosage and Administration). However, as there is insufficient clinical data for pediatric populations under age 5, Ditropan is not recommended for this age group.”

The labeling for the extended release tablets indicates that “Ditropan XL is also indicated in the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).” In addition the label states “the pharmacokinetics of Ditropan XL were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of Ditropan XL in these pediatric patients were consistent

with those reported for adults.” and “Ditropan XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (See Dosage and Administration).”

The labeling for the oxybutynin transdermal patch indicates that “the pharmacokinetics of oxybutynin and N-desethyloxybutynin were not evaluated in individuals younger than 18 years of age.” and “the safety and efficacy of Oxytrol in pediatric patients have not been established.”

Pediatric exclusivity for the active moiety was granted on February 8, 2002.

**3. AERS Search Results:** Oxybutynin (including all dosage forms: immediate release tablets and syrup, extended release tablets and Oxytrol™ transdermal patch).

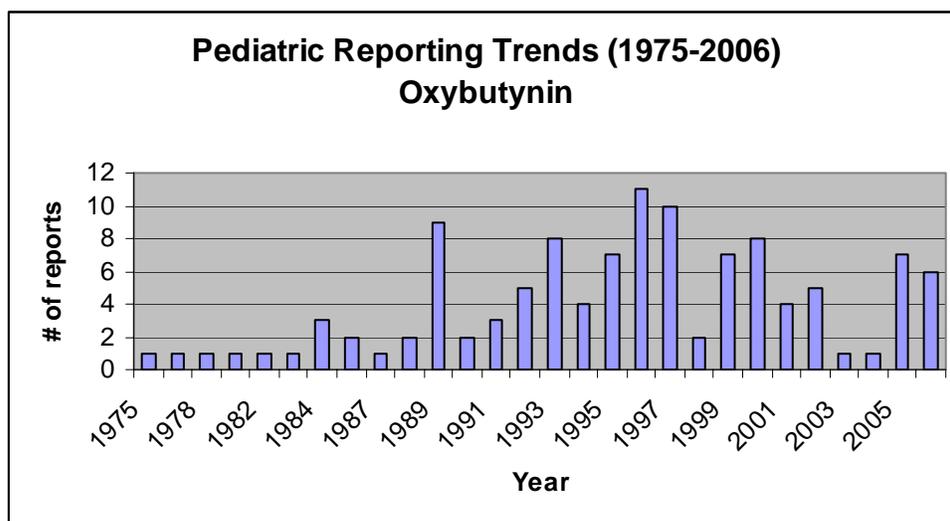
**3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)**

<b>Table 1: Crude counts<sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date to Present (July 1975 - August 30, 2006) (US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	1288 (1072)	1056 (853)	66 (46)
Pediatrics (0-16 yrs.)	114 (88)	51 (28)	1 (1)*
Age unknown (Null values)	237 (210)	125 (104)	20 (17)
Total	1639 (1370)	1232 (985)	87 (64)

<sup>1</sup> May include duplicates  
<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

\* not a pediatric death – the patient was an adult whose age was entered into AERS erroneously as “6”

**Figure 1: Reporting trend for pediatric reports from approval date**



**3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)**

<b>Table 2: Crude counts<sup>1</sup> of AERS Reports for All Sources from date Pediatric Exclusivity was Granted to Present</b> (55 month period: February 8, 2002 - August 30, 2006) (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	430 (303)	397 (271)	53 (39)
Pediatrics (0-16 yrs)	20 (9) 6 (1) - first 13 mos of Peds Exclus. 14 (8) – from 13 mos to present	18 (7) 6 (1) - first 13 mos of Peds Exclus. 12 (6) - from 13 mos to present	0 (0)
Age unknown (Null Values)	79 (64)	63 (48)	16 (14)
Total	529 (376)	478 (326)	69 (53)
<sup>1</sup> May include duplicates			
<sup>2</sup> Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.			

**4. Postmarketing Review of All Pediatric Adverse Event Reports received since oxybutynin received pediatric market exclusivity.**

**4.1 Case Characteristics:** The characteristics of the 15 unduplicated pediatric cases received since oxybutynin was granted pediatric exclusivity are presented below in Table 3.

<b>Table 3: Characteristics of pediatric cases reported from date Pediatric Exclusivity was Granted to Present</b> (February 8, 2002 - August 30, 2006) N=15	
Gender [n=15] (no. of cases)	Male: 10 Female: 5
Age [n=15] (no. of cases)	0- <1 month : 0 1 month <2 yrs: 3 2-5 yrs: 2 6-11 yrs: 10 12-16 yrs: 0 Mean 6.8 years; Median 9 years; Range 15 mos to 10 years
Origin [n=13] (no. of cases)	US – 7, Foreign – 6
Event date [n=14] (no. of cases)	1997 - 1    2003 - 1 1998 - 1    2005 - 4 2000 - 1    2006 - 3 2002 - 3
Daily dose [n=7] (no. of cases)	Average 9mg , Median 5mg , Range 5-21mg *
Duration of therapy [n= 10]	Average 160 days, Median 42 days Range: 12 hrs to 2 years

<b>Table 3: Characteristics of pediatric cases reported from date Pediatric Exclusivity was Granted to Present (February 8, 2002 - August 30, 2006) N=15</b>	
Indications [n=11 ] (no. of cases)	Nocturnal enuresis -4 Neurogenic bladder-3 Enuresis-1 Detrusor muscle spasms-1 Urinary frequency-1 None (accidental ingestion)-1
Outcomes (no. of cases)	Hospitalization-5, Disability-2, Life-Threatening-1, Other-5

\* one case (ISR# 4054208, Mfr# 3200221340GDDC) stated the daily dose was 37.5mg but had erroneously assumed a syrup concentration of 5mg/ml (concentration is actually 5mg/5ml), therefore for the purposes of this review we considered the daily dose to be 7.5mg

#### 4.2 Summary of Cases received since post-pediatric exclusivity was granted

Most of the patients were 6 to 11 years of age and the most common indication was nocturnal enuresis (an unapproved indication). It is noted that although oxybutynin is not recommended for children under the age of five years, 5 of the 15 patients in this case series were younger than five years. The indications for use in the patients younger than five years were neurogenic bladder (1), detrusor muscle spasms (1), hypospadias surgery (1), unknown (1), and none/accidental ingestion (1).

There were no pediatric death reports. Thirteen of the 15 cases were considered serious by regulatory definition (hospitalization-5, disability-2, life-threatening-1, other-5). Of the 13 serious cases, the following 7 cases were confounded by other drugs/underlying conditions or did not contain enough information to make a causality assessment:

ISR#	Age	Event(s)	Confounders/comments
4975071	10 yrs	Hypoglycemia	Primary suspect med: desmopressin Pt has underlying insulin dependent diabetes
4345187	9 yrs	Cough	Pt had recent nasal surgery Pt has underlying cystic fibrosis Numerous co-suspect medications reported
4711204	9 yrs	Malignant hyperthermia	Primary suspect med: levetiracetam Pt had been on oxybutynin several years
3877225	10 yrs	Hyponatremia	Primary suspect med: desmopressin Pt recovered after only desmopressin dc'd
4950793	10 yrs	Thrombocytopenia	History of thrombocytopenia w/propiverine Leukemia was suspected but not confirmed
5848771	7 yrs	Elevated LFTs	Pt was in hospital for gastroenteritis Very little information provided
3967354	2 yrs	Stopped breathing, coma	Hx of tracheostomy, ventriculoperitoneal shunt at 4 mos, quadriplegia Very little information provided

The remaining 6 serious cases are presented below.

1. Case #3797797, ISR#3935913, Mfr#EMADSS2002003499 Switzerland 2002- Disability

An anxious 10 year old male was started on Ditropan tablets 5mg/day (divided into 3 doses) for nocturnal enuresis in June 2001. His bladder capacity was about half of that expected for his age. In the autumn he started having difficulties falling asleep, had night terrors with panic attacks, during which he might bite and hit himself. He imagined that he saw monsters, little green men with a large knife who threatened him, and had the impression of being followed. In March 2002 he started to become depressed and had ideas of suicide. There may have been several possibly stressful events in his life. Sleep improved after the withdrawal of oxybutynin in April 2002. Atarax syrup (for sleep) and Risperdal (for depression) were prescribed one month prior to discontinuation of Ditropan.

2. Case #3805625, ISR#3955993, Mfr#13485 US 2002 – Other: Medically Significant

A 4 year old female born with brain damage began treatment with Ditropan in April 1998 (up to 21mg daily) for bedwetting. Within 6 months to a year she experienced behavioral events described as irritability with high levels of anxiety, and sensitivity to light and noise. She also became overheated, did not sweat, had a red face and extremities, and dry hands and mouth. About a year and a half after starting oxybutynin therapy, Paxil was added and the dose increased to 15 mg daily. She became violent and a danger to herself and others and had personality changes. Paxil dose was tapered and discontinued, but the patient became depressed and suicidal. Paxil was resumed at half the dose, and Ditropan XL 5mg was started. The patient's symptoms improved, but the wetting accidents persisted. Ditropan XL was discontinued and Detrol 1 mg twice a day was started. All symptoms resolved. Paxil was discontinued, but the withdrawal symptoms reappeared. Paxil was restarted at 5 mg daily. As of 2002 the patient therapy with Paxil was ongoing and "the neurogenic bladder symptoms had improved as the patient physically matured."

3. Case #3846608, ISR#3983099, Mfr#ALZ6372 US 2002 – Other: Medically Significant

A 9 year old female had a seizure while on therapy with Ditropan XL 5mg daily (duration unknown), and was treated in the ER. That day the patient had ingested a tablespoon of Benadryl. Therapy with Ditropan XL continues, and the patient remains seizure free.

4. Case #5877112, ISR #4762204, Direct report US 2005 – Disability

An 8 year old female began treatment with Ditropan XL 5mg daily for urinary frequency in December 2004. In January 2005 she began to exhibit symptoms of obsessive thinking, acted confused and sometimes became hallucinogenic. The symptoms increased in frequency and intensity over the next few months. In April 2005 she was seen by a psychiatrist and Ditropan XL was discontinued. Within 3 days a significant improvement in her condition was noted.

5. Case #5986462, ISR #4914364, Mfr#2006AP000071 Canada 2006 – Other: Medically Significant

A 10 year old male who had been treated for 2 years with Strattera (atomoxetine) for ADHD began treatment with oxybutynin 3.75mg twice daily on December 23, 2005 for nocturnal enuresis. Five days later, on December 28, 2005 the patient experienced extrapyramidal side effects manifested by "locking of the neck 30 degrees to the right, locking of jaw, and babbling speech like a mentally retarded person". In addition, the patient also experienced tachycardia (130-140bpm), difficulty breathing, facial swelling and jaw pain. The patient was taken to the ER and treated with diphenhydramine and acetaminophen, with resolution of the symptoms 15 minutes after treatment. X-rays showed no evidence of a spinal lesion. Oxybutynin was discontinued. No recurrence of symptoms has occurred. The patient had a previous history of mandibular dislocation.

6. Case #6056158, ISR #5008565, Mfr#RB-2770-2006 France 2006 – Hospitalization

A 15.5 month old female accidentally ingested medications from her Grandfather's medication box. Several hours later her parents found that she was difficult to wake up and had trouble breathing. She was transferred to an emergency pediatric unit and then to the ICU. Toxicology tests suggested the patient was intoxicated with buprenorphine and possibly oxybutynin. She experienced hypoglycemia, urinary retention, drowsiness, miosis, tachycardia, dyspnea and fever. She was treated with an infusion of glucose 5% and paracetamol (150mg four times a day). The patient recovered and was discharged 3 days later.

### **Unlabeled serious events:**

One serious case reported extrapyramidal effects (locking of jaw and neck at 30 degree angle, babbling speech). Extrapyramidal disorder is not labeled, therefore a search for other cases in the AERS database was conducted (using the Higher Level Term “dystonias” and the Preferred Term “extrapyramidal disorder”). Two other cases (ISR# 1782145, ISR# 1649426) in pediatric patients were found but a direct relationship to oxybutynin was unclear. The first case appeared temporally related to azithromycin treatment and reported the extrapyramidal symptoms abated after azithromycin alone was discontinued. The second case reported a worsening of preexisting facial dystonia in a 10 year old male with neurogenic bladder. The event did not abate after oxybutynin was discontinued.

More definitive cases are needed to further explore an association between oxybutynin and extrapyramidal reactions.

### **Labeled serious events:**

Five serious cases reported events that may be due to anticholinergic effects of oxybutynin, particularly anticholinergic CNS excitation (hallucinations, irritability, insomnia). Overall there are a disproportionate number of CNS excitation reports since approval in pediatric patients versus adult patients. An AERS search was conducted to compare the number of reports of CNS excitation in pediatric patients vs. adult patients. At least one of the following preferred terms was reported in 28% of the pediatric reports (32/114) vs. 7.6% of the adult reports (99/1286):

#### **Preferred Terms indicative of CNS excitation:**

<i>Abnormal dreams</i>	<i>Hallucination</i>	<i>Panic reaction</i>
<i>Aggression</i>	<i>Hallucination, visual</i>	<i>Psychomotor hyperactivity</i>
<i>Agitation</i>	<i>Initial insomnia</i>	<i>Restlessness</i>
<i>Anger</i>	<i>Insomnia</i>	<i>Sleep disorder</i>
<i>Anxiety</i>	<i>Irritability</i>	<i>Sleep terror</i>
<i>Attention deficit/hyperactivity disorder</i>	<i>Middle insomnia</i>	<i>Sleep walking</i>
<i>Emotional disorder</i>	<i>Nervousness</i>	<i>Tremor</i>
<i>Excitability</i>	<i>Panic attack</i>	

## **5. Summary/Recommendations**

Fifteen unduplicated pediatric cases have been received since pediatric exclusivity was granted. Most of the patients were 6 to 11 years of age and the most common indication was nocturnal enuresis (an unapproved indication). It is noted that although oxybutynin is not recommended for children under the age of five years, 5 of the 15 patients in this case series were younger than five years. Better communication to the treating community regarding approved indications and age-groups appear to be needed.

No deaths were reported. Thirteen of the 15 cases were serious. Seven of the 13 serious cases appeared related to other drugs/underlying conditions or did not contain enough

information to attribute causality to oxybutynin. One of the 6 remaining serious cases reported an extrapyramidal reaction (an unlabeled event) in a 10 year old boy; however more definitive cases are needed to further explore an association between oxybutynin and extrapyramidal reactions.

The 5 remaining serious cases reported labeled events that may be due to anticholinergic effects of oxybutynin, particularly anticholinergic CNS excitation (hallucinations, irritability, insomnia). Overall there are a disproportionate number of CNS excitation reports since approval in pediatric patients versus adult patients. Consideration should be given for adding text to the label that emphasizes the potential for pediatric patients to develop CNS excitation following oxybutynin treatment since discontinuation of oxybutynin alone may correct the CNS excitation (if this in fact a drug adverse reaction), and the pediatric patient may not need further treatment of CNS excitation with other pharmaceuticals.

**Safety Evaluator's Signature/Date:** /s/Paula Gish/9-14-06

**\*\*\*\*\*Appendix\*\*\*\*\***

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

PID#: D030161

DATE: April 29, 2003

FROM: Evelyn R. Farinas, R.Ph., M.G.A.  
Post Marketing Safety Evaluator  
Division of Drug Risk Evaluation (DDRE), HFD-430

THROUGH: Mark Avigan, M.D., Acting Director, DDDRE, HFD-430

TO: Solomon Iyasu, M.D., M.P.H., Team Leader  
Division of Pediatric Drugs and Development, HFD-960  
Office of Counter-Terrorism and Pediatric Development

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Ditropan Tablets, Syrup and Ditropan XL (oxybutynin chloride tablets, syrup and extended release tablets) NDA 17-577, NDA 18-211 and NDA 20-897)  
Pediatric Exclusivity Approval Date: February 8, 2002

**EXECUTIVE SUMMARY**

Ditropan tablets, syrup and extended release tablets were approved in July 1975, November 1979 and December 1998, respectively, for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency urinary leakage, urge incontinence, dysuria). Pediatric exclusivity for the active moiety was granted on February 8, 2002. Since the earliest approval date in 1975, AERS has received a total of 930 reports listing a Ditropan product as suspect drug. In the interval between February 8, 2002 and March 19, 2003 FDA received five pediatric reports, where the majority were from the US and all had a serious outcome. Even though the majority of reported adverse events were unlabeled, the frequency of reporting for each event was small. The causality for the adverse events in these five cases cannot be attributed solely to Ditropan therapy. The concomitant use of other drugs (e.g., desmopressin, Benadryl and Paxil), overdosing or underlying conditions may have contributed to the adverse events.

**1. AERS Search Results: Ditropan Tablets, Syrup and Extended Release Tablets**

AERS was searched for all adverse event reports submitted to FDA since the earliest approval date for a Ditropan product (i.e., July 1975, Ditropan tablets) until March 19, 2003 and listed the trade name Ditropan or Ditropan XL as the suspect product. The search included domestic and foreign reports that. The search was also stratified by age groups and by dates relative to the February 2002 Pediatric Exclusivity date. Another broader search was done to capture cases listing any oxybutynin product as the suspect drug in the pediatric population (0-16 years of age) since the Pediatric Exclusivity date was done.

**A. From earliest approval date (i.e., July 16, 1975) to March 19, 2003:**

**1. Counts of reports (figures are derived from line listings, and may include duplicate and follow up reports):**

**Table 1 – AERS reports counts [July 1975 through March 2003]**

\*\*\*to see table – please refer to PDF version of this document in DFS \*\*\*

**Reporting trend for pediatric reports from approval date (July 1977- March 2003):**

\*\*\*to see graph – please see PDF version of this document in DFS \*\*\*

Highest frequency of reporting to AERS occurred in 1996 and 1997 with ten and nine reports per year, respectively. Range of pediatric reporting frequency from 1977 to 2003 was 1 to 10, with only one report per year submitted in 11 of the 26 years since approval. Following pediatric exclusivity (i.e., between February 8, 2002 and March 19, 2003) there have been 5 pediatric reports submitted to AERS.

**2. Top 20 reported preferred terms (PT) and labeling status of these events (asterisk indicates that the event is mentioned in the Adverse Events, Warnings, Precautions or Overdosage section of the label):**

**All ages:**

Dry Mouth*	129	Hallucination NOS*	36
Dizziness (Exc. Vertigo)*	60	Vision Blurred*	35
Diarrhoea NOS*	52	Condition Aggravated	32
Constipation*	49	Confusion*	32
Drug Ineffective	45	Pruritus NOS	32
Nausea*	45	Dyspepsia*	31
Headache NOS*	40	Vision Abnormal NOS*	26
Sedation*	40	Oedema Peripheral	25
Abdominal Pain NOS	37	Asthenia*	2
Dermatitis NOS*	36	Vomiting NOS*	21

**Adults:**

Dry Mouth*	108	Dyspepsia*	29
Dizziness (Exc. Vertigo)*	57	Pruritus NOS	29
Diarrhoea NOS*	44	Confusion*	27
Constipation*	41	Condition Aggravated	26
Nausea*	40	Dermatitis NOS*	26
Headache NOS*	38	Hallucination NOS*	24
Abdominal Pain NOS	34	Oedema Peripheral	24
Drug Ineffective	33	Vision Abnormal NOS*	22
Sedation	32	Dry Eye NOS*	19
Vision Blurred*	31	Pain NOS*	18

**Peds:**

Hallucination NOS*	7	Agitation	3
Dermatitis NOS	5	Asthenia*	3
Pyrexia*	5	Confusion*	3
Tachycardia NOS*	5	Diplopia	3
Convulsions NOS*	4	Loss of Consciousness*	3
Diarrhoea NOS*	4	Skin disorder NOS	3
Drug Interaction NOS	4	Vasodilatation*	3
Personality Disorder NOS	4	Vertigo	3
Thinking Abnormal	4	Abdominal Pain Upper	2
Abdominal Pain NOS	3	Abnormal Dreams	2

**B. From Pediatric Exclusivity approval date (February 8, 2002) to March 19, 2003:**

**1. Counts of reports:**

\*\*\*to see table – please refer to PDF version of this document in DFS \*\*\*

The same number of cases (i.e., five unique cases) were retrieved from AERS for the pediatric population since the Pediatric Exclusivity date, regardless of whether a Ditropan product or a generic oxybutynin product was listed as suspect drug.

**2. Top 20 reported PT and labeling status of these events (asterisk denotes event is labeled in the Adverse Events, Warnings, Precautions or Overdosage section):**

**All ages:**

Drug Ineffective	4	Drug Interaction NOS	2
Convulsions NOS*	3	Dysphagia	2
Depression NOS	3	Erythema	2
Dry Eye NOS*	3	Eye Haemorrhage NOS	2
Dry Mouth*	3	Hallucinations, Visual*	2
Dyspnoea NOS	3	Intraocular Pressure Increased	2

Vision Blurred*	3	Medication Error	2
Atrial Fibrillation	2	Panic Reaction	2
Condition Aggravated	2	Abdominal distension	1
Dizziness (Exc. Vertigo)*	2	Abdominal Pain Upper	1

**Adults:**

Drug Ineffective	4	Abdominal Distention	1
Dry Eye NOS*	3	Abdominal Pain Upper*	1
Dyspnoea NOS	3	Blindness Transient	1
Vision blurred*	3	Blood Calcium Increased	1
Atrial Fibrillation	2	Breast Engorgement	1
Condition Aggravated	2	Cardiac Arrest	1
Dizziness (Ex. Vertigo)*	2	Cardiac Disorder NOS	1
Dry Mouth*	2	Cardiac Failure Congestive*	1
Dysphagia	2	Cerebrovascular Accident NOS	1
Eye Haemorrhage NOS	2	Chest Pain	1

**Pediatrics:**

Depression NOS	2	Convulsions NOS*	1
Hallucination, Visual*	2	Depression Suicidal	1
Panic Reaction	2	Drug Interaction NOS	1
Abnormal Behavior NOS	1	Drug Withdrawal Syndrome	1
Acidosis NOS	1	Dry Mouth*	1
Aggression	1	Electroencephalogram Abnormal	1
Anger	1	Erythema	1
Anxiety Nec	1	Flushing*	1
Bladder Disorder NOS	1	Hyperacusis	1
Blood Osmolarity Decreased	1	Hyponatremia	1

**2. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after pediatric exclusivity approval (February 8, 2002 to March 19, 2003 (N=5 unduplicated cases)**

**A. Demographics:**

Gender: Female (2), Male (3)

Age: 0-<1 mo. (0)  
 1 mo.- <2 years (0)  
 2-5 years (2)  
 6-11 years (3)  
 12-16 years (0)

Origin: US (3), Belgium (1), Switzerland (1)

Outcome: Death (0), Hospitalization (1), Other (4, of which 3 were medically significant and 1 was disability)

Indications:       Enuresis (1)  
                      Nocturnal enuresis (1)  
                      Neurogenic bladder (1)  
                      Detrusor muscle spasms (1)  
                      Not stated (1)  
Doses:       Range, 5-37.5 mg per day (N=4)

## **B. Labeling status of the top 20 adverse events; comparison to the adult adverse event profile.**

### **1. Labeling information**

The labeling for the immediate release tablets and syrup indicates that “the safety and efficacy of DITROPAN administration have been demonstrated for pediatric patients 5 years of age and older (see Dosage and Administration). However, as there is insufficient clinical data for pediatric populations under age 5, Ditropan is not recommended for this age group”. The labeling for the extended release tablets indicates that “the pharmacokinetics of DITROPAN XL® were not evaluated in individuals younger than 18 years of age” and that “the safety and efficacy of DITROPAN XL® in pediatric patients have not been established”.

### **2. AERS review**

Since granting Pediatric Exclusivity in February 2002, there have been few reports entered into AERS for the adult (29) and pediatrics groups (5). The majority of the reports for both population groups were of domestic origin and had a serious outcome. Even though the majority of reported adverse events in each group were unlabeled, the frequency of reporting for each event was small.

Several unlabeled cardiac and gastrointestinal (GI) events were reported with a greater frequency in the adult group. However, cardiac and GI events are known to occur with oxybutynin due to its anticholinergic properties. The Precautions and Adverse Events sections of the Ditropan and the Ditropan XL labels indicate that oxybutynin may aggravate the symptoms of coronary heart disease, congestive heart failure, tachycardia and cardiac arrhythmias. While abdominal distention is not specifically mentioned in the labeling, flatulence is listed under the Adverse Reactions section of the Ditropan XL labeling. The most frequently reported event in the adult group was drug ineffectiveness. Neither the Ditropan nor the Ditropan XL label lists the number or percentage of patients in clinical trials who discontinued therapy due to drug ineffectiveness.

A noticeable number (8/20) of psychiatric adverse events were reported in the pediatric group. Oxybutynin’s anticholinergic central nervous system excitation and overdosing may be involved in the development of the reported adverse events. Overdosing was reported in two patients that were treated with Ditropan syrup, a 10-year old on 37.5 mg daily and a 4-year old whose daily dose was 21 mg. The maximum recommended

pediatric dose is 15 mg per day. While many of the reported adverse events are not specifically mentioned (i.e., aggression, anxiety, anger, depression and suicidal depression), the labeling for Ditropan Syrup or Ditropan XL lists insomnia, restlessness, tremor, irritability, delirium, nervousness and confusion under the **Adverse Reactions** and **Overdosage** sections.

Dry mouth was reported in both adults and pediatric populations.

**C. Comments and analysis of any events not recognized for adult population.**

The majority of the 20 most frequently reported adverse events in the adult population since February 8, 2002, may be attributed to the anticholinergic properties of oxybutynin.

**D. Comments and analysis of any events uniquely identified in pediatrics but not reported in the adult population, including increased frequency of any expected events.**

There were no unique events to the pediatric population. Psychiatric adverse events have also been reported in adults.

**E. Comments on increased frequency reporting of any expected events.  
Recommended actions.**

None

**F. Summary and comments on death reports.**

There were no fatalities reported in the pediatric population.

**G. Summary of all pediatric reports during period.**

The causality for the adverse event in the five cases received since granting Pediatric Exclusivity to Ditropan products cannot be attributed solely to Ditropan therapy. The concomitant use of other drugs, overdosing or underlying conditions may have contributed to the adverse events.

For instance, hyponatremia has been reported in two pediatric patients using desmopressin to treat primary nocturnal enuresis <sup>1</sup>. Water intoxication, hyponatremia and decrease in plasma osmolality may also occur with desmopressin use, although rarely<sup>2</sup>. As an ethanolamine antihistamine, Benadryl (diphenhydramine) may show greater anticholinergic activity than other antihistamines. Anticholinergic effects may be potentiated when antihistamines and other anticholinergic drugs are used together <sup>3</sup>. The safety and effectiveness of Paxil (paroxetine) in the pediatric population has not been established, but in adults, anxiety, nervousness, depersonalization, emotional lability, hostility and antisocial reactions were observed in clinical trials in adult patients <sup>4</sup>.

**Table 1 – Summary of Pediatric Adverse Event Reports in AERS since February 8, 2002**

*\*\*\*to see table – please refer to PDF version of this document in DFS \*\*\**

**Summary**

There were few reports of AEs in Pediatric Subjects submitted to the FDA listing a Ditropan product as a suspect drug since granting Pediatric Exclusivity on February 8, 2002. In the five reports in patients 16 years of age or less, the causality for the adverse events cannot be attributed solely to Ditropan therapy. The concomitant use of other drugs, overdosing or underlying conditions may have contributed to the adverse events.

Evelyn R. Farinas, R.Ph., M.G.A.

Concur:

Debra Boxwell, Pharm. D.

cc:

HFD-430/Avigan/Boxwell

1. American Hospital Formulary Service (2001), Hormones and Synthetic Substitutes 68:00, Pituitary 68.28
2. Mosby's Drug Consult –12th Edition (2002) Section II-Drug Information, "D" drug information, desmopressin acetate
3. US PDI Drug Information for the Health Care Professional, 22nd Edition (2002), "A" monographs, antihistamines
4. Electronic PDR, Paxil drug labeling, 2003 edition

**Standard Searches:**

A. Adults (17 years and above)

1. All outcomes from AP date (no set criteria)
2. Serious outcomes from AP date
3. Death as an outcome from AP date
4. All outcomes from PE date to present or any desired date
5. Serious outcomes from PE date to present or any desired date
6. Death as an outcome from PE date to present or any desired date

B. Ages 0-16 years ONLY

1. Same as above 1-6
2. Retrieve case reports for hands-on review

**Standard Printouts for Attachments:**

A. Adults (17 years and above)

1. Frequency counts of all preferred terms (PT) in cases
2. Frequency counts of all PT in cases with serious outcomes

3. Frequency counts of all PT in cases with death as an outcome
4. Frequency counts of cases by Gender and ages

B. Ages 0-16 years

1. Frequency counts of all preferred terms (PT) in cases
2. Frequency counts of all PT in cases with serious outcomes
3. Frequency counts of all PT in cases with death as an outcome
4. Frequency counts of cases by Gender and ages

## **Drug Product Information**

### **Adverse Events with DITROPAN XL®**

The safety and efficacy of DITROPAN XL® was evaluated in a total of 580 participants who received DITROPAN XL® in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 2). The adverse events are reported regardless of causality.

### **Table 2: Incidence (%) of Adverse Events Reported by $\geq 5\%$ of Patients Using DITROPAN XL® (5-30 mg/day)**

\*\*\*to see table – please refer to PDF version of this document in DFS \*\*\*

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL® were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related. The discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%. In addition, the following adverse events were reported by 2 to  $<5\%$  of patients using DITROPAN XL® (5-30 mg/day) in all studies. *General*: abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular*: hypertension, palpitation, vasodilatation; *Digestive*: flatulence, gastroesophageal reflux; *Musculoskeletal*: arthritis; *Nervous*: insomnia, nervousness, confusion; *Respiratory*: upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin*: dry skin, rash; *Urogenital*: impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

### **Adverse Events with Oxybutynin Chloride**

Other adverse events have been reported with oxybutynin chloride: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, and suppression of lactation.

## **OVERDOSAGE**

The continuous release of oxybutynin from DITROPAN XL® should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a

cathartic may be administered.

Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

### **Limitations of the Adverse Event Reporting System (AERS)**

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

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Evelyn Farinas  
5/8/03 10:12:12 AM  
CSO  
Mark Avigan  
5/8/03 10:32:22 AM  
MEDICAL OFFICER

\*\*\*\*\*END of APPENDIX\*\*\*\*\*

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/s/

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9/15/2006 11:56:45 AM  
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang  
9/15/2006 01:20:27 PM  
MEDICAL OFFICER