

**MEMORANDUM**

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

**PID#:** D050371

**DATE:** September 6, 2006

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**SUBJECT:** 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Glimepiride (Amaryl®)  
NDA: 020-496  
Pediatric Exclusivity Approval Date: June 9, 2005

**1.0 Executive Summary**

The Adverse Event Reporting System (AERS) database was searched for reports of adverse events (serious and non-serious) occurring with the use of glimepiride (Amaryl®) in pediatric patients. Up to the "data lock" date of July 8, 2006, AERS contained 1494 reports for glimepiride (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.54 % of the total (8/1494).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, June 9, 2005 to June 9, 2006. We used an AERS data lock date of July 8, 2006, to allow time for reports received up to June 9, 2006, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 290 reports (raw counts, all ages, foreign and domestic, as well as those with no

information on age and country of origin). Pediatric reports represent approximately 0.69% of the total number of reports (2/290). We will refer to this 13-month interval as the *pediatric exclusivity period* in the remainder of this review.

Our search of AERS resulted in 2 pediatric cases associated with glimepiride therapy during the pediatric exclusivity period of June 9, 2005 through July 8, 2006. No fatal pediatric cases were identified for any time period for glimepiride.

Both of the identified cases were associated with unlabeled adverse events and were serious in nature. One case involved a 17-year-old female who experienced behavioral abnormalities after 2 doses of glimepiride. The other case involved a newborn male who experienced various congenital anomalies after *in utero* exposure. However, it is difficult to assess an association of the resulting adverse events to the use of glimepiride from only two cases.

This review does not reveal any new safety concerns for the use of glimepiride in pediatric patients. DDRE will continue to monitor adverse events associated with the use of glimepiride in pediatric patients.

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## 2.0 Products, Indications, Pediatric Labeling, and Pediatric Filing History

### 2.1 Products:<sup>1</sup>

Drug Name / FDA Application Number	Approval Date	Dosage Form / Route	Strength	Marketing Status	Company
Amaryl® / NDA # 020496	Nov. 30, 1995	Tablet / Oral	1 mg, 2 mg, 4 mg	Prescription	Sanofi Aventis US

### 2.2 Indications:<sup>2</sup>

Amaryl® is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with non-insulin dependent (Type 2) diabetes mellitus whose hyperglycemia cannot be controlled by diet and exercise alone. Amaryl® may be used concomitantly with metformin when diet, exercise, and Amaryl® or metformin alone does not result in adequate glycemic control. In addition, Amaryl® is approved for combination therapy with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

### 2.3 Pediatric Labeling:<sup>3</sup>

Pediatric use and effects are addressed in the following sections of the label:

#### a) CLINICAL PHARMACOLOGY, Special Populations:

*Pediatric.* The pharmacokinetics of glimepiride (1 mg) were evaluated in a single dose study conducted in 30 Type 2 diabetic patients (Male = 7; Female = 23) between ages 10 and 17 years. The mean AUC<sub>(0-last)</sub> (338.8±203.1 ng•hr/mL), Cmax (102.4±47.7 ng/mL) and T1/2(3.1±1.7 hours) were comparable to those previously reported in adults (AUC<sub>(0-last)</sub> 315.2±95.9 ng•hr/mL, Cmax 103.2±34.3 ng/mL and T1/2 5.3±4.1 hours).

#### b) PRECAUTIONS, Pregnancy:

*Teratogenic Effects.* Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats

<sup>1</sup> Drugs@FDA. U.S. FDA, CDER. Amaryl® (glimepiride), NDA 020496. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=AMARYL>. Accessed: August 2006.

<sup>2</sup> Drugs@FDA. U.S. FDA, CDER. Labeling Information, Amaryl® (glimepiride), NDA 020496. Available at: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApapprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApapprovalHistory). Accessed: August 2006.

<sup>3</sup> Drugs@FDA. U.S. FDA, CDER. Labeling Information, Amaryl® (glimepiride), NDA 020496. Available at: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApapprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApapprovalHistory). Accessed: August 2006.

when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride. There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, AMARYL (glimepiride tablets) should not be used during pregnancy. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

*Nonteratogenic Effects.* In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride. Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

**Nursing Mothers** – In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether AMARYL is excreted in human milk, other sulfonylureas are excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, and because of the effects on nursing animals, AMARYL should be discontinued in nursing mothers. If AMARYL is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above Pregnancy, Nonteratogenic Effects.)

**Pediatric Use** – The safety and efficacy of AMARYL were evaluated in an active-controlled, single-blind (patients only), 24-week trial involving 272 pediatric patients, ranging from 8 to 17 years of age, with Type 2 diabetes. AMARYL (n=135) was administered at 1mg initially, and then titrated up to 2, 4 or 8 mg (mean last dose 4 mg) until the therapeutic goal of self-monitored fasting blood glucose < 7.0 mmol/L (< 126 mg/dl) was achieved. The active comparator metformin (n=137) was administered at 500 mg twice daily initially and titrated up to 1000 mg twice daily (mean last dose 1365 mg).

HbA1c (%)	Naïve Patients*		Previously Treated Patients*	
	Metformin	AMARYL	Metformin	AMARYL
	69	72	57	55
Baseline (mean)	8.2	8.3	9.0	8.7
Change from baseline (mean)+	-1.2	-1.0	-0.2	0.2
Adjusted Treatment Difference** (95% CI)		0.2 (-0.3; 0.7)		0.4 (-0.4; 1.2)

- Intent-to-treat population (AMARYL, n=127; metformin, n=126)

+ - Change from baseline means are least square means adjusting for baseline HbA1c and Tanner Stage

\*\* - Difference is AMARYL – metformin with positive differences favoring metformin

The profile of adverse reactions in pediatric patients treated with Amaryl was similar to that observed in adults.

Hypoglycemic events, as documented by blood glucose values <36 mg/dL, were observed in 4% of patients treated with AMARYL and in 1% of patients treated with metformin.

Weight (kg)	Metformin*	AMARYL*
Baseline (mean)	67.3	66.5
Change from baseline (mean)+	0.7	2.0
Adjusted Treatment Difference** (95% CI)		1.3 (0.3; 2.3)

\*- Safety population with on-treatment evaluation for weight (AMARYL, n=129; metformin, n=126)

+ - Change from baseline means are least square means adjusting for baseline HbA1c and Tanner Stage

\*\* - Difference is AMARYL – metformin with positive differences favoring metformin

### c) ADVERSE REACTIONS

#### **Pediatric Patients**

In a clinical trial, 135 pediatric patients with Type 2 diabetes were treated with AMARYL. The profile of adverse reactions in these patients was similar to that observed in adults.

### d) DOSE AND ADMINISTRATION

#### **Specific Patient Populations**

AMARYL (glimepiride tablets) is not recommended for use in pregnancy or nursing mothers. Data are insufficient to recommend pediatric use of AMARYL.

### 2.4 Pediatric Filing History.<sup>4,5</sup>

A Written Request (WR) was issued for this drug on December 31, 2001. The WR was

<sup>4</sup> Written Request Archives, E-I, glimepiride-Amaryl. FDA, CDER, Pediatric and Maternal Health Staff.  
[http://cdernet/pediatrics/ArchivePedsOct2004/WRITTEN\\_REQUESTS\\_ARCHIVE.HTM#E-I](http://cdernet/pediatrics/ArchivePedsOct2004/WRITTEN_REQUESTS_ARCHIVE.HTM#E-I). Accessed: August 2006.

<sup>5</sup> Aljuburi, L. Regulatory Project Manager Review, NDA 20-496/S-015. Available in the Division Files System. Accessed: August 2006.

subsequently amended on August 23, 2002; November 13, 2003; and April 14, 2004.

On March 14, 2005, the sponsor submitted Supplement 015 as their response to the WR, as amended, with two study reports. Study 1 was a single-dose pharmacokinetics study, entitled "An open-label, multicenter, single-dose study to evaluate the pharmacokinetics of glimepiride (Amaryl) in pediatric patients with type 2 diabetes mellitus" (HOE 490/4045). Study 2 was a clinical trial of 24-weeks duration comparing glimepiride monotherapy versus metformin monotherapy in pediatric patients with Type 2 diabetes, entitled "Glimepiride versus Metformin as Monotherapy in Pediatric Subjects with Type 2 Diabetes Mellitus: A Single Blind Comparison Study" (HOE 490/4038).

An approvable action letter was issued on September 15, 2005, citing labeling deficiencies in the package insert. The complete response to the approvable letter was submitted on October 31, 2005.

**3.0 AERS Search Results: Glimepiride (Amaryl®)**

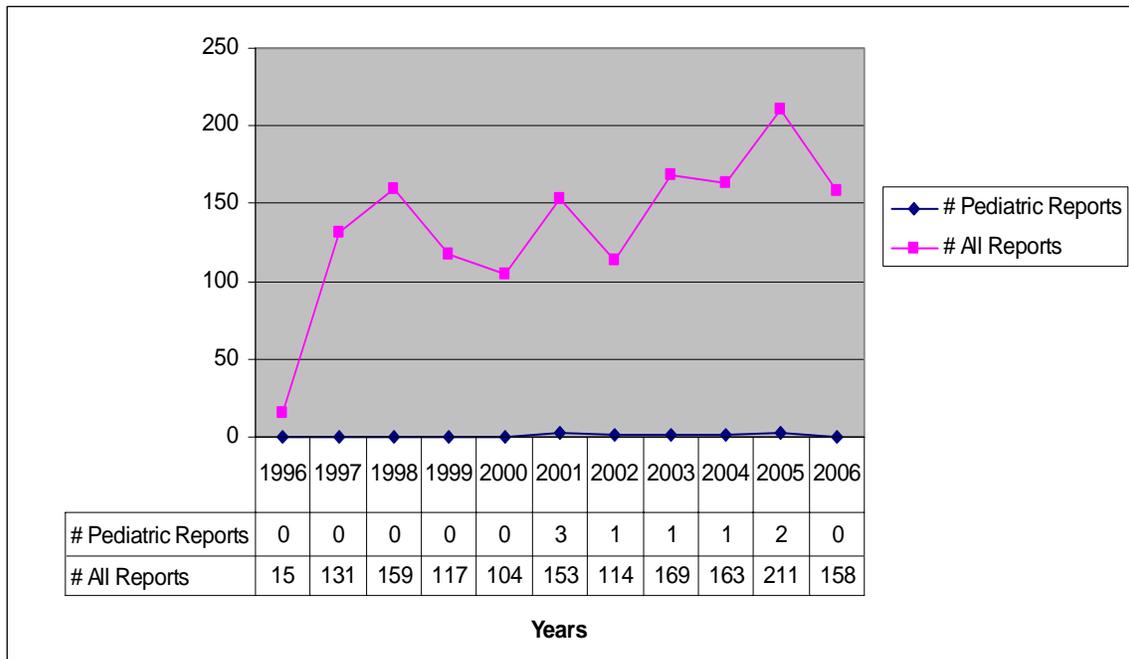
**3.1 Table 1: Crude Count of Reports - AERS Searches include all sources, U.S. & foreign, from marketing approval date (November 30, 1995) through AERS cut-off date (July 8, 2006)**

<b>Table 1: Crude Counts<sup>1</sup> of AERS Reports for Glimepiride from All Sources from Marketing Approval Date (November 30, 1995) through AERS cut-off date (July 8, 2006)</b> <i>(US counts in parentheses)</i>			
	<b>All reports (US)</b>	<b>Serious<sup>2</sup> (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs.)	1225 (377)	1112 (292)	153 (30)
Pediatrics (0-16 yrs.)	8 (3)	8 (3)	0 (0)
Age unknown (Null values)	261 (185)	194 (124)	21 (11)
<i>Total</i>	<i>1494 (565)</i>	<i>1319 (419)</i>	<i>175 (41)</i>

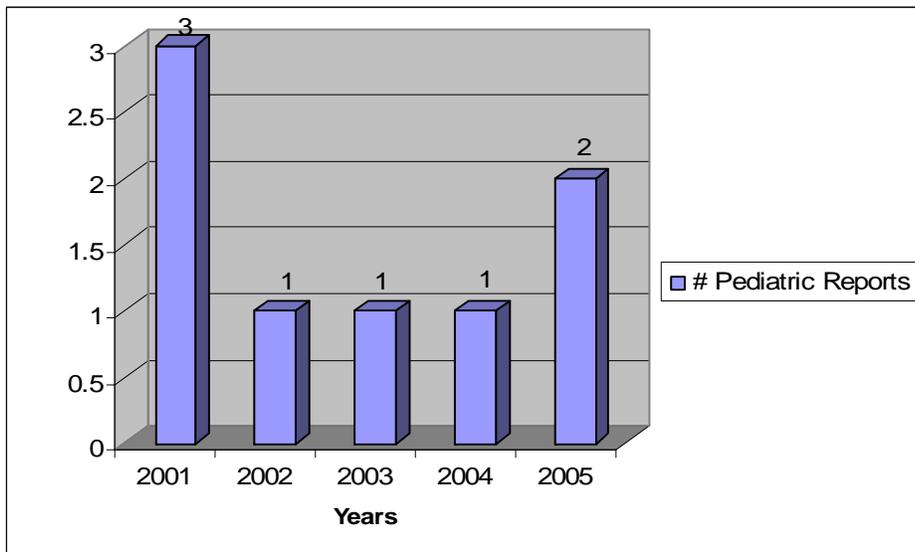
<sup>1</sup>May include duplicates

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

**Figure 1: Reporting trend for all reports (N=1494) from approval (November 30, 1995) through AERS cut-off date (July 8, 2006)**



**Figure 2: Reporting trend for all pediatric reports (n=8) from approval (November 30, 1995) through AERS cut-off date (July 8, 2006)**



**3.2 Table 2: Crude Count of Reports - AERS Searches include all sources, U.S. & foreign, from Pediatric Exclusivity approval date (June 9, 2005) through AERS cut-off date (July 8, 2006)**

<b>Table 2: Crude Counts<sup>1</sup> of AERS Reports for Glimepiride from All Sources from date Pediatric Exclusivity was Granted (June 9, 2005) through AERS cut-off date (July 8, 2006)</b> <i>(US counts in parentheses)</i>			
	<b>All reports (US)</b>	<b>Serious<sup>2</sup> (US)</b>	<b>Death (US)</b>
Adults (≥ 17 yrs.)	261 (83)	240 (67)	31 (9)
Pediatrics (0-16 yrs)	2 (1)	2 (1)	0 (0)
Age unknown (Null Values)	27 (17)	20 (13)	0 (0)
<i>Total</i>	<i>290 (101)</i>	<i>262 (81)</i>	<i>31 (9)</i>

<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.

**4.0 Postmarketing Review of All Pediatric Adverse Event Cases received during the one-year after a drug receives pediatric market exclusivity.**

**4.1 Case Characteristics:**

<b>Table 3: Characteristics of Pediatric Cases reported during the pediatric exclusivity approval through AERS cut-off date (June 9, 2005 through July 8, 2006)</b> <b>N=2</b>	
<u>Gender</u>	
Female	1
Male	1
<u>Age at time of event</u>	1 day, 17 years
<u>Origin</u>	
US	1
Foreign	1
<u>Event date</u>	
2003	1
2005	1
<u>Time to Event, (days)</u>	n=1 2 days
<u>Indications</u>	
Diabetes mellitus	1
Exposure via Maternal Use	1

**Table 3: Characteristics of Pediatric Cases reported during the pediatric exclusivity approval through AERS cut-off date (June 9, 2005 through July 8, 2006)**  
N=2

Outcomes <sup>†</sup>	
Congenital Anomaly	1
Disability	1
Other	1

<sup>†</sup> Outcomes are not mutually exclusive; one case could contain more than one outcome.

**4.2 Summary of Cases received during the 1-year post-pediatric exclusivity period:**

**4.2.1. Fatal Cases, n=0**

Our search of AERS resulted in 2 pediatric cases associated with glimepiride therapy. No fatal pediatric cases were identified for any time period for glimepiride.

**4.2.2 Non-Fatal Cases, n=2**

**4.2.2.1 Unlabeled/Unexpected Cases**

Two non-fatal cases associated with unlabeled adverse events were identified. These cases are summarized below. The unlabeled events are underlined.

**ISR #: 4802157, Domestic (*Behavioral Abnormalities*):**

A 17-year-old female started glimepiride 1 mg daily on September 28, 2005, for treatment of diabetes mellitus after stopping metformin therapy on September 27, 2005. In addition to diabetes, her medical history is positive for asthma, Down syndrome, and open-heart surgery as a baby. Her concomitant medications included amitriptyline, rabeprazole, and albuterol. Prior to glimepiride therapy on September 22, 2005, the patient was prescribed metformin 500 mg daily. After a few days of metformin therapy, the patient’s school contacted her mother stating “that her daughter had been acting up in school and doing things out of the ordinary, like leaving class and wandering in the halls”. After the first dose of glimepiride, the mother stated that her daughter started “losing her memory and became absentminded”. The patient was given a second dose of glimepiride by her mother who then discontinued it because of the above described adverse events. On October 3, 2005, unspecified laboratory tests and computed tomography scan were reported normal. The reported adverse events were not treated with medications. At time of reporting, the patient’s abnormal behavior persisted, and she was forced to stay out of school.

**ISR #: 4803446, Foreign (*Congenital Anomalies*):**

A newborn male, who was exposed *in utero* to glimepiride, was born on May 30, 2003, with microcephaly, cardiopathy (ventricular septal defect), and face malformations including “coarse facies, large ears, oblique upper palpebral

cleft, long philtrum". His mother had taken glimepiride (dose and regimen were not reported) for one year until the 5<sup>th</sup> week of amenorrhea (from January 1, 2001 through September 1, 2002). The pregnancy was diagnosed on September 9, 2002. The report stated that the mother was also taking 2 other unspecified insulin products. The mother had 9 previous pregnancies resulting in: 1 elective abortion, 3 spontaneous abortions, 3 healthy children, and 2 children who were born with congenital anomalies and subsequently died (the first died at 7-month-old had normal karyotype, cardiopathy, and short limbs, and the second died at 9-day-old [unreported type of anomaly]). The family history included consanguinity as the mother was married to her first cousin. No other relevant information was provided.

#### 4.2.2.2 Analysis of Cases

In the case of *in utero* exposure, it is difficult to determine from a spontaneous reporting system such as AERS whether the events were due to exposure to glimepiride, the mother's underlying medical conditions<sup>6,7</sup>, or the family history of parental consanguinity. Parental consanguinity is a strong risk factor for this newborn's birth defects. Khalid et al stated that "after controlling for confounders, first cousin consanguinity remained significantly associated with an increased risk of congenital heart defects (CHD): infants born to first cousin marriages had a 1.8 times higher risk of having a CHD diagnosed at birth compared to those born to unrelated parents (95% CI: 1.1-3.1)".<sup>8</sup> Their published results showed that first-cousin marriage was a significant risk factor for ventricular septal or atrial septal defect, hypoplastic left heart, and single ventricle.<sup>8</sup>

In the case of the 17-year-old, concomitant drug therapies, her history of Down syndrome, or a combination of both could have been contributory to the patient's adverse events. In addition to glimepiride, this patient also took amitriptyline which suggests some emotional or depressive imbalance. People with Down syndrome are often challenged with various behavioral disorders such as temper tantrums, aggression, oppositional behavior, anxiety, and depression.<sup>9</sup>

In addition, the association of amitriptyline to patient's behavioral disorders can not be ruled out because amitriptyline labeling warns about an increased risk of suicidal thinking in children and adolescents with the use of antidepressants including amitriptyline. The warning also states that "patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior".<sup>10</sup>

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<sup>6</sup> Wren C et al. Cardiovascular malformations in infants of diabetic mothers. *Heart*. 2003 Oct;89(10):1217-20.

<sup>7</sup> Galindo A et al. Outcome of fetuses in women with pregestational diabetes mellitus. *J Perinat Med*. 2006;34(4):323-31.

<sup>8</sup> Khalid Y, Ghina M, Fadi B, Fadi C, May K, Joseph R, Makhoul G, Hala T. Consanguineous marriage and congenital heart defects: a case-control study in the neonatal period. *Am J Med Genet A*. 2006 Jul 15;140(14):1524-30.

<sup>9</sup> National Down Syndrome Society. Development, Behavioral Guidelines. Available at: <http://www.ndss.org/content.cfm?fuseaction=InfoRes.Devarticle&article=210>. Accessed: August 2006.

<sup>10</sup> Drug Facts and Comparisons 4.0, online. Monograph: Amitriptyline hydrochloride. Available at: <http://online.factsandcomparisons.com/index.aspx>. Accessed: August 2006.

Furthermore, while the events identified in this case are unlabeled events, they are similar to events identified in the AERS reports for adults (n=261) during the pediatric exclusivity period (June 9, 2005 through July 8, 2006). The adverse events identified for the adults include, but are not limited to, emotional disorder (1), mental status changes (1), thinking abnormal (1), amnesia (2), and abnormal behaviour (3).

## **5.0 Summary/Recommendations**

There were 2 non-fatal cases of adverse events associated with the use of glimepiride during the 1-year pediatric exclusivity period in AERS. While both cases were of a serious nature, it is still difficult to assess an association of the resulting adverse events to glimepiride therapy from only two cases.

This review did not reveal any new safety concerns for the use of glimepiride in pediatric patients. We will continue to monitor adverse events associated with the use of glimepiride in pediatric patients.

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Joslyn Swann, Pharm.D.  
Safety Evaluator

Concur:

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Lanh Green, Pharm.D., M.P.H.  
Team Leader

## **Appendix 1**

### **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.

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/s/

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