MEMORANDUM

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

PID # D040849

DATE: March 9, 2006

TO: Solomon Iyasu, MD, MPH., Acting Deputy Director
Division of Pediatric Drug Development

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Office of the Commissioner

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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Rosiglitazone (Avandia®), NDA# 21-071
Pediatric Exclusivity Approval Date: 12/09/2004

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1. EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events occurring with the use of rosiglitazone (Avandia) in pediatric patients. Between the marketing approval date (5/25/1999) and data lock date of January 9, 2006, AERS contained a total of 9072 rosiglitazone reports. Of these 9072 cases, 14 cases (0.15 %) involved pediatric patients – two of which were reported during the one-year post-pediatric exclusivity period (December 9, 2004 –January 9, 2006).

The two cases reported during the one-year post-pediatric exclusivity period were from the United States and neither reported a serious outcome. The first case involved accidental ingestion by a 22-month-old male and the second involved a 12-year-old female who experienced behavioral changes (became "promiscuous" and "ran away") while taking rosiglitazone/metformin (Avandamet) for type 2 diabetes. The 12-year-old was switched to rosiglitazone but the behaviors continued. Rosiglitazone was changed to metformin and the caretaker believes the behaviors are "not as bad" but could be due to "being a teenager."

The 12 pediatric cases reported *prior* to the one-year post-pediatric exclusivity consisted of six accidental ingestions in children 15 months to 5 years of age, four in utero exposures, and two reports of elevated liver function tests. Four of the six accidental ingestions were associated with hypoglycemia or seizures and required medical attention. The four reports of in utero exposures involved a child with "left breast tissue development" identified at 6-months of age, twins with fetal stress and premature delivery from a 40-year old female on multiple medications (including atorvastatin, metformin, acarbose, felodipine, and perindopril), and twins with premature delivery and multiple significant medical problems. Rosiglitazone is labeled Pregnancy Category C. The first of the two reports of elevated liver function tests involved a 16-year-old, 420-pound female who experienced "liver function tests three times the normal limit" while taking rosiglitazone (dose and duration of therapy not known). Rosiglitazone was discontinued and "her liver function tests returned to normal." The second of the two reports involved an 11-year-old male with a history of obesity and type 2 diabetes with normal ALT (17) and AST (23) findings in May 1997. Rosiglitazone 2 mg daily was initiated on March 3, 2000. On March 28, the ALT was elevated at 63. On December 15, 2000, the ALT was 109, AST was 44, and GGT remained within normal limits. There was no jaundice or liver enlargement. Rosiglitazone was discontinued. On January 16, 2001, ALT was 240, AST 85, and bilirubin was normal. Hepatitis serology testings were negative. On January 20, Epstein Barr virus antibody panel showed EBV IgG and nuclear antigen were positive, and EBV IgM antibody negative. The abdominal ultrasound showed hepatomegaly with fatty infiltration. On February 6, transaminase values were decreasing (ALT 189, AST 78). Rosiglitazone labeling contains information regarding elevated liver function tests, recommendations for monitoring, and guidelines for discontinuation of therapy.

Since marketing approval, FDA has received one report (in July 2003) of pediatric death associated with rosiglitazone. The report was an in utero exposure (exposure time about 5 weeks during the first trimester) and involved a male twin who was born three months premature and experienced multiple medical problems (including congestive heart failure

and liver failure). The cause of death was "respiratory failure secondary to ascites from liver failure."

In summary, our search of the AERS database identified 14 pediatric rosiglitazone cases reported to FDA since marketing in 1999. These 14 cases report different events such as accidental ingestion, in utero exposure, elevated liver function tests, and behavior changes. However, there are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. The Division of Drug Risk Evaluation will continue to monitor.

2. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

2.1 Rosiglitazone Products Available in the United States (Table 1)[1]

Table 1. Description of Rosiglitazone Products Available in the United States.		
Product	**US Approval Date**	**Tablet Strengths**
Rosiglitazone (Avandia®)	5/25/99	2, 4, and 8 mg
Metformin/Rosiglitazone (Avandamet®)	10/10/02	500 mg/1 mg, 500mg /2 mg, 500 mg/4 mg, 1000 mg/2 mg, 1000 mg/4 mg
Glimepiride/Rosiglitazone (Avandaryl®)	11/23/05	1 mg/4 mg, 2 mg/4 mg, 4 mg/4 mg,

2.2 Rosiglitazone Approved Indications (Table 2)[2]

Table 2 describes FDA-approved indications for rosiglitazone products. Per the most recent approved labeling on July 29, 2005, there are no approved pediatric indications.

Table 2. Rosiglitazone FDA-Approved Indications. Source: 7/29/2005 Approved Labeling.			
Indication	**Avandia®**	**Avandamet®**	**Avandaryl®**
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus: ▪ As monotherapy ▪ In combination with a sulfonylurea, metformin or insulin ▪ In combination with sulfonylurea plus metformin	X		
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus ▪ Those already on combination of rosiglitazone and metformin ▪ Those not adequately controlled on metformin alone		X	
Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes ▪ Those already on combination of rosiglitazone and sulfonylurea ▪ Those not adequately controlled on a sulfonylurea alone ▪ Those who initially responded to rosiglitazone alone and require additional glycemic control			X

[1] The Electronic Orange Book. Silver Spring (MD): Food and Drug Administration. c2006 – [cited 2006 Feb 27]. Available from: www.fda.gov/cder/ob/default.htm.

[2] Avandia, Avandamet, and Avandaryl FDA-Approved Labeling. Drugs@FDA. Silver Spring (MD): Food and Drug Administration. c2006 – [cited 2006 Feb 27]. Available from: www.accessdata.fda.gov/scripts/cder/drugsatfda.

2.3 Rosiglitazone Labeling

2.3.1 Pediatric Mentions in Rosiglitazone (Avandia) Labeling (Source: 7/29/05 approved labeling)

Clinical Pharmacology, Special Populations, *Pediatric:*
Pharmacokinetic parameters of rosiglitazone in pediatric patients were established using a population pharmacokinetic analysis with sparse data from 96 pediatric patients in a single pediatric clinical trial including 33 males and 63 females with ages ranging from 10 to 17 years (weights ranging from 35 to 178.3 kg). Population mean CL/F and V/F of rosiglitazone were 3.15 L/hr and 13.5 L, respectively. These estimates of CL/F and V/F were consistent with the typical parameter estimates from a prior adult population analysis.

Precautions, General, *Weight Gain*:
In a 24-week study in pediatric patients aged 10 to 17 years treated with AVANDIA 4 to 8 mg daily, a median weight gain of 2.8 kg (25th, 75th percentiles: 0.0, 5.8) was reported.

Precautions, General, *Hematologic:*
White blood cell counts also decreased slightly in adult patients treated with AVANDIA. Small decreases in hemoglobin and hematocrit have also been reported in pediatric patients treated with AVANDIA. The observed changes may be related to the increased plasma volume observed with treatment with AVANDIA and may be dose related (see ADVERSE REACTIONS, Laboratory Abnormalities, *Hematologic*).

Precautions, Pediatric Use
After placebo run-in including diet counseling, children with type 2 diabetes mellitus, aged 10 to 17 years and with a baseline mean body mass index (BMI) of 33 kg/m2, were randomized to treatment with 2 mg twice daily of AVANDIA (n = 99) or 500 mg twice daily of metformin (n = 101) in a 24-week, double-blind clinical trial. As expected, fasting plasma glucose (FPG) decreased in patients naïve to diabetes medication (n = 104) and increased in patients withdrawn from prior medication (usually metformin) (n = 90) during the run-in period. After at least 8 weeks of treatment, 49% of AVANDIA-treated patients and 55% of metformin-treated patients had their dose doubled if FPG >126 mg/dL. For the overall intent-to-treat population, at week 24, the mean change from baseline in HbA1c was -0.14% with AVANDIA and -0.49% with metformin. There was an insufficient number of patients in this study to establish statistically whether these observed mean treatment effects were similar or different. Treatment effects differed for patients naïve to therapy with antidiabetic drugs and for patients previously treated with antidiabetic therapy (Table below).

Week 24 FPG and HbA1c Change from Baseline Last-Observation-Carried Forward in Children with Baseline HbA1c >6.5%.

	Naïve Patients		Previously-Treated Patients	
	Metformin	Rosiglitazone	Metformin	Rosiglitazone
N	40	45	43	32
FPG (mg/dL)				
Baseline (mean)	170	165	221	205
Change from baseline (mean)	-21	-11	-33	-5
Adjusted Treatment Difference* (rosiglitazone–metformin)†		8		21
(95% CI)		(-15, 30)		(-9, 51)
% of patients with =30 mg/dL decrease from baseline	43%	27%	44%	28%
HbA1c (%)				
Baseline (mean)	8.3	8.2	8.8	8.5
Change from baseline (mean)	-0.7	-0.5	-0.4	0.1
Adjusted Treatment Difference* (rosiglitazone – metformin)†		0.2		0.5
(95% CI)		(-0.6, 0.9)		(-0.2, 1.3)
% of patients with =0.7% decrease from baseline	63%	52%	54%	31%

*Change from baseline means are least squares means adjusting for baseline HbA1c, gender, and region.
†Positive values for the difference favor metformin.

Treatment differences depended on baseline BMI or weight such that the effects of AVANDIA and metformin appeared more closely comparable among heavier patients. The median weight gain was 2.8 kg with rosiglitazone and 0.2 kg with metformin (see PRECAUTIONS, General, *Weight Gain*).
Fifty four percent of patients treated with rosiglitazone and 32% of patients treated with metformin gained ≥2 kg, and 33% of patients treated with rosiglitazone and 7% of patients treated with metformin gained ≥5 kg on study.

Adverse events observed in this study are described in ADVERSE REACTIONS.

Adverse Reactions, Pediatrics

AVANDIA has been evaluated for safety in a single, active-controlled trial of pediatric patients with type 2 diabetes in which 99 were treated with AVANDIA and 101 were treated with metformin. In this study, one case of diabetic ketoacidosis was reported in the metformin group. In addition, there were 3 patients in the rosiglitazone group who had FPG of <300 mg/dL, 2+ ketonuria, and an elevated anion gap. The incidence and type of adverse events reported in ≥5% of patients for each treatment group are shown below.

Adverse Events Reported by ≥5% of Patients in a Double-Blind, Active-Controlled, Clinical Trial With AVANDIA or Metformin as Monotherapy in Pediatric Patients

Preferred Term	AVANDIA N = 99 %	Metformin N = 101 %
Headache	17.2	13.9
Influenza	7.1	5.9
Upper Respiratory Tract Infection	6.1	5.9
Cough	6.1	5.0
Hyperglycemia	8.1	6.9
Dizziness	5.1	2.0
Back Pain	5.1	1.0
Nausea	4.0	10.9
Hypoglycemia	4.0	5.0
Nasopharyngitis	3.0	11.9
Vomiting	3.0	8.9
Abdominal Pain	3.0	6.9
Pharyngolaryngeal pain	2.0	5.0
Diarrhea	1.0	12.9
Sinusitis	1.0	5.0
Dysmennorhea	0	6.9

Adverse Reactions, Laboratory Abnormalities, *Hematologic:*
In a single study in pediatric patients, decreases in hemoglobin and hematocrit (mean decreases of 0.29 g/dL and 0.95%, respectively) were reported.

Dosage and Administration, Special Populations *Pediatric:*
Data are insufficient to recommend pediatric use of AVANDIA.

2.3.2 Safety-Related Updates to Product Labeling During the One-Year Post-Pediatric Exclusivity Period

Macular Edema
In December 2005, the sponsor and FDA notified healthcare professionals about post-marketing reports of new onset and worsening diabetic macular edema for patients receiving rosiglitazone. In the majority of these cases, the patients also reported concurrent peripheral edema. In some cases, the macular edema resolved or improved following discontinuation of therapy and in one case, macular edema resolved after dose reduction.[3] The Dear Healthcare Provider letter can be viewed at: www.fda.gov/medwatch/safety/2006/Avandia_DHCPletter.pdf

[3] Medwatch 2006 Safety Alerts. Silver Spring (MD): Food and Drug Administration. c2006 – [cited 2006 Feb 28]. Available from: http://www.fda.gov/medwatch/safety/2006/safety06.htm#Avandia.

Patient Information Leaflet
In May 2005, a labeling revision provided for a Patient Information Leaflet for rosiglitzone (Avandia) tablets. The Patient Information Leaflet can be viewed at: http://www.fda.gov/cder/foi/label/2005/021071s010lbl.pdf.

Labeling Revisions to Precautions, Drug Interactions, and Adverse Reactions
In January 2005, revisions were made to the CLINICAL PHARMACOLOGY section, PRECAUTIONS section, Drug Interactions subsection, and ADVERSE REACTIONS section of the rosiglitazone (Avandia) and metformin/rosiglitazone (Avandamet) package insert labels. The letter and labeling revisions can be viewed at: http://www.fda.gov/cder/foi/appletter/2005/21071s014,21410s009ltr.pdf and http://www.fda.gov/cder/foi/label/2005/21071s014lbl.pdf.

2.4 Pediatric Filing History

Table 3 below contains relevant regulatory activity excerpted from the Medical Officer's April 15, 2005 Clinical Review for the NDA pediatric supplement.[4]

Table 3. Relevant Regulatory Activity for Pediatric Use of Rosiglitazone.

Date	Regulatory Activity
5/25/1999	Approval letter for rosiglitazone (Avandia®) requires submission of pediatric drug development plan within 120 days and grants deferral for submission of required pediatric assessment until 12/2/2000
9/21/1999	Sponsor submits Proposed Pediatric Study Request – including proposed pediatric development plan for award of pediatric exclusivity and pediatric assessment. Placebo-controlled monotherapy study proposed.
2/1/2000	FDA/Division of Metabolic and Endocrine Products (DMEP) issues Written Request for pediatric study with metformin as active control. Sponsor counter-proposes combination or second-line study in a teleconference, but ultimately active control monotherapy trial was agreed upon. Submission date was specified as 4/30/2002.
9/30/2004	Sponsor submits study report (NDA 21-071 S15 SE5) for Study 207 (24-week, randomized, double-blind, active-controlled clinical trial in children ages 8-17 years with Type 2 diabetes mellitus) to support FDA's granting of Pediatric Exclusivity, a proposed new indication for use of rosiglitazone in children with type 2 diabetes, and additional proposed pediatric labeling.
12/9/2004	Pediatric Exclusivity granted.
7/29/2005	Labeling revised to include results of study comparing the effects of Avandia to those of metformin in children with type 2 diabetes mellitus, aged 10-17 years. In the supplemental application approval letter, FDA indicated a pediatric indication for the use of Avandia was not supported by the results of the submitted study.

[4] Zawadzki, JK. Clinical Review of Rosiglitazone (NDA pediatric supplement, 21-071 S-015 SE5). 2005 Apr 15.

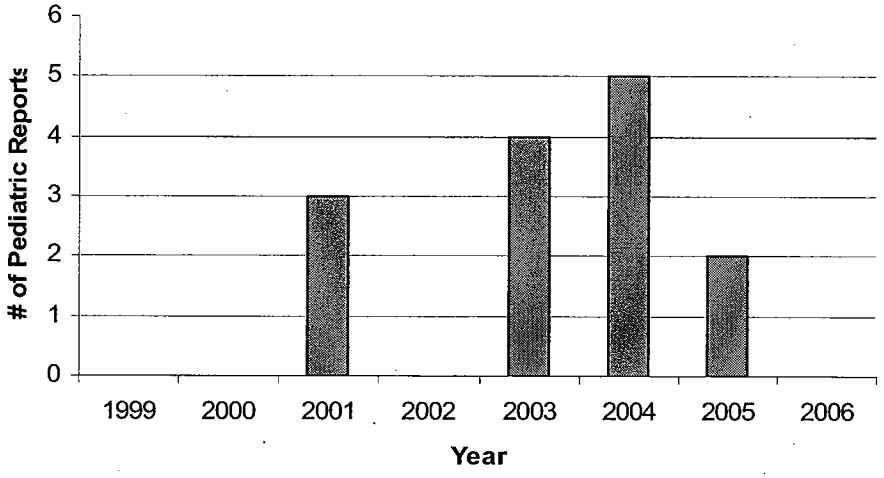
3. AERS SEARCH RESULTS: ROSIGLITAZONE

3.1 Count of Reports: AERS Search Including All Sources (U.S. & Foreign) From Marketing Approval Date (Table 4)

Table 4. Crude counts[1] of AERS Reports for All Sources from Marketing Approval Date (5/25/99) through AERS Cutoff (1/9/06)			
Age	**All reports (US)**	**Serious[2] (US)**	**Death (US)**
Adults (≥ 17 yrs)	6496 (5318)	3058 (1923)	319 (175)
Peds (0-16 yrs)	14 (13)	10 (9)	1 (1)
Age Unknown (Null)	2562 (2356)	773 (570)	45 (24)
Total	9072 (7687)	3841 (2502)	365 (200)

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

Figure 1: Reporting Trend For Pediatric Reports (approval date through 1/9/06)



3.2 Count of Reports: AERS Search Including All Sources (U.S. & Foreign) From Pediatric Exclusivity Approval Date (Table 5)

Table 5. Crude counts[1] of AERS Reports for All Sources from Date Pediatric Exclusivity Was Granted (12/9/04) through AERS Cutoff (1/9/06)			
Age	**All reports (US)**	**Serious[2] (US)**	**Death (US)**
Adults (≥ 17 yrs)	907 (657)	487 (242)	41 (17)
Peds (0-16 yrs)	2 (2)	0 (0)	0 (0)
Null	480 (417)	192 (129)	9 (4)
Total (all ages)	1389 (1076)	679 (371)	50 (21)

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

4. POSTMARKETING REVIEW OF PEDIATRIC ADVERSE EVENT REPORTS

4.1 Case Characteristics:

Table 6. Characteristics of Pediatric Rosiglitazone Reports in the AERS Database (Marketing through AERS Cutoff Date of January 9, 2006)

Characteristic	Pediatric Exclusivity Approval to AERS Cutoff Date (12/9/04 - 1/9/06)	Marketing To Pediatric Exclusivity Approval (5/25/99 - 12/9/04)	Total Reports (5/25/99-1/9/06)
Number of Unique Reports	**2**	**12**	**14**
Origin of Reports			
United States	2	11	13
Foreign	0	1	1
Year (FDA Receive Date)			
2001	-	3	3
2002	-	0	0
2003	-	4	4
2004	-	5	5
2005	2	-	2
Gender			
Male	1	7	8
Female	1	5	6
Unknown	0	0	0
Age At Event			
0 - <1 month	0	3	3
1 month - 2 years	1	6	7
3 – 5 years	0	1	2
6 - 11 years	0	1	2
12 – 16 years	1	1	3
Unknown	0	0	0
Indication For Use			
Type 2 Diabetes	1	1	2
Unknown Indication	0	1	1
Other (Accidental Ingestion, In Utero Exposure)	1	10	11
Primary Reported Adverse Event			
Accidental Ingestion (Hypoglyemia/Seizures/Vomiting)	1	6	7
Behavioral Changes	1	0	1
Elevated LFTs	0	2	2
In utero exposure	0	4	4
Doses, Reported (Daily)			
2 mg	0	1	1
4 mg	1	2	3
8 mg	0	2	2
Unknown	1	7	8
Reported Outcomes			
Congenital Anomaly	0	0	0
Death	0	1	1
Disability	0	0	0
Hospitalization	0	5	5
Life-Threatening	0	0	0
Required Intervention	0	0	0
Other	0	4	4
Unknown/Not Reported	2	2	4

4.2 Summary of Cases Received

FDA received two pediatric rosiglitazone cases during the one-year post-pediatric exclusivity period. Both cases were from the United States, and neither case reported a serious outcome. The first case (**CASE 5843245**) reported an accidental ingestion by a 22-month-old male and the second (**CASE 5843212**) involved a 12-year-old female who experienced behavioral changes (became "promiscuous" and "ran away") while taking rosiglitazone/metformin (Avandamet) for type 2 diabetes. The 12-year-old was switched to rosiglitazone but the behaviors continued. Rosiglitazone was changed to metformin and the caretaker believes the behaviors are "not as bad" but indicated the behaviors could be due to "being a teenager." Over the past two years, the 12-year-old also received oxycarbazepine (Trileptal), buproprion (Wellbutrin), spironolactone, trazodone, and levothyroxine (Synthroid).

Because FDA received only two pediatric rosiglitazone cases during the post-pediatric exclusivity period, a review of all pediatric rosiglitazone cases in the AERS database received between marketing approval (5/25/1999) and the pediatric exclusivity period (12/9/04) was performed. FDA received 12 reports during this period, 11 of the reports were from the United States and one report was from Europe. Six reports involved accidental ingestion, of which four reports were associated with hypoglycemia and seizures (hypoglycemia: 1 report, seizure: 1, hypoglycemia and seizure: 2). There were four reports associated with in utero exposure (child with "left breast tissue development" identified at 6-months of age: 1 report, twins with fetal stress and premature delivery from a 40-year old female on multiple medications (including atorvastatin, metformin, acarbose, felodipine, and perindopril): 1 report, and twins with premature delivery and multiple significant medical problems: 2 reports). The remaining two reports were associated with elevated liver function tests. The first of these two reports (**CASE 3751264**) involved a 16-year-old, 420-pound female who experienced "liver function tests three times the normal limit" while taking rosiglitazone (dose and duration of therapy not known). Rosiglitazone was discontinued and "her liver function tests returned to normal." The second of the two reports (**CASE 3616428**) involved an 11-year-old male with a history of obesity, type 2 diabetes, hypogonadism, bilateral slipping of capital femoral epiphysis, and headaches. This 11-year-old had normal ALT (17) and AST (23) findings in May 1997. Rosiglitazone 2 mg daily was initiated on March 3, 2000. On March 28, 2000, the ALT was elevated at 63 (reference range: 0-40), AST 37 (reference range 0-37), and GGT was 34 (reference range 11-51). On December 15, 2000, the ALT was 109, AST was 44, and GGT remained within normal limits. There was no jaundice or liver enlargement. Rosiglitazone was discontinued. On January 16, 2001, ALT was 240, AST 85, GGT elevated at 82, and bilirubin was normal. Hepatitis serology testings were negative. On January 20, Epstein Barr virus antibody panel showed EBV IgG and nuclear antigen were positive, and EBV IgM antibody negative. The abdominal ultrasound showed hepatomegaly with fatty infiltration. On February 6, 2001, ALT was decreased to 189, AST 78, and GGT 72. On February 14, 2001, it was reported the "ALT is decreasing." The FDA-approved rosiglitazone labeling contains information regarding elevated liver function tests, recommendations for monitoring, and guidelines for discontinuation of therapy.

Since marketing approval, FDA has received one report of pediatric death associated with rosiglitazone (**CASE 3923489**, received July 2003). An attorney reported the death of a 6-month-old male twin who was born three months premature and experienced multiple medical problems (including congestive heart failure and liver failure). The cause of death was "respiratory failure secondary to ascites from liver failure." The mother was 26-years-of-age with a history of "inability to conceive" and received clomiphene and metformin. Due to unspecified intolerance, metformin was switched to rosiglitazone 4 mg daily. The in utero exposure time to rosiglitazone was about five weeks. There was no history of diabetes mellitus in the mother and the indication for metformin and rosiglitazone was not provided. However, insulin-sensitizing agents such as metformin and rosiglitazone are thought to reduce circulating insulin levels in women with polycystic ovary syndrome (PCOS) and restore normal reproductive function.[5] The FDA-approved labeling classifies rosiglitazone as Pregnancy Category C (there are no adequate or well-controlled studies in pregnant women; rosiglitazone should not be used in pregnancy unless benefit justifies potential risk to fetus).

Characteristics for all the pediatric cases found in the AERS database are described in Table 6 above and a summary of each case in ATTACHMENT 1.

4.3 Limitation of AERS

It is possible there are additional pediatric rosiglitazone adverse event reports. The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the United States reflects underreporting and duplicate reporting. For any given report, there is limited 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.

5. SUMMARY AND RECOMMENDATIONS

In summary, our search of the AERS database identified 14 pediatric rosiglitazone cases reported to FDA since marketing in 1999. These 14 cases report different events such as hypoglycemia related to accidental ingestion, in utero exposure, elevated liver function tests, and behavior changes. However, there are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. We will continue to monitor.

Jo Wyeth, Safety Evaluator

Lanh Green, Team Leader

Rosemary Johann-Liang, Deputy Director

[5]The Practice Committee of the American Society for Reproductive Medicine. Use of insulin sensitizing agents in the treatment of polycystic ovary syndrome. 2004 Sep;82(Supp 1):181-182.

6. **ATTACHMENT 1:** Summary of Pediatric Rosiglitazone (Avandia) Cases Found in AERS Database, Categorized by Date Received (Marketing through AERS Cutoff Date of January 9. 2006)

No.	FDA Rcvd Date	Case Description
1.	7/22/05	**CASE 5843212: 12-year-old female experiences behavioral changes** *Consumer (primary caregiver) reports her 12-year-old granddaughter started rosiglitazone/metformin (Avandamet) for type 2 diabetes and experienced behavioral changes (became "promiscuous" and "ran away"). After about one year (on May 21, 2004), the child was switched to rosiglitazone (Avandia) but the behaviors continued. In 2005, rosiglitazone was discontinued and the child started metformin (Glucophage). The grandmother thought the behaviors were "not as bad" after stopping rosiglitazone but admitted the behaviors could be attributed to "being a teenager" (although her "granddaughter is a quiet type"). Concurrent medications over the past two years included: spironolactone, trazodone, levothyroxine (Synthroid), buproprion (Wellbutrin), and oxcarbazepine (Trileptal). Follow up with the grandmother indicated the child is currently taking only oxcarbazepine and metformin.*
2.	7/22/05	**CASE 5843245: 22-month-old male with accidental ingestion** *Pharmacist reports a 22-month-old male accidentally ingested one rosiglitazone 4 mg tablet on September 24, 2004 while staying at his grandparents. The child was sick with a fever and ear infection prior to ingesting the tablet, and vomited within 30 minutes of ingestion but no tablet remnants were identified in the emesis. The pharmacist noted the child had not exhibited "any other symptoms since taking it around 8:30 AM: (time of report unknown). Final outcome not reported.*
3.	3/4/04	**CASE 4100890: 2-year-old female with accidental exposure** *American Association of Poison Control Centers reported that a 2-year-old female may have accidentally ingested rosiglitazone (co-suspects include bupropion, metformin and atorvastatin). At an unknown time following the possible ingestion, the child experienced a seizure while showering with her mother and another subsequent seizure. The attending physician reported the child's glucose, CBC and electrolytes were within normal limits.*
4.	1/30/04	**CASE 4075527: 2-year-old-male with accidental ingestion** *American Association of Poison Control Centers reported that a 2-year-old male may have ingested rosiglitazone or glyburide (both were available in the home). The child could not be awakened and was taken to the emergency room where his serum glucose was 29 mg/dL. Dextrose solution was administered, serum glucose was 62 mg/dL the following morning and the child was discharged.*
5.	1/23/04	**CASE 4070182: 23-month-old female with accidental ingestion** *American Association of Poison Control Centers reported a 23-month-old may have accidentally ingested rosiglitazone (amount unknown) and experienced episodes of hypoglycemia (including one associated with a seizure). The child was treated at the emergency room with dextrose infusion and discharged after remaining normoglycemic for 24 hours. The parent was on rosiglitazone and the child's babysitter was also taking an oral hypoglycemic. It was unknown which product, or if any was ingested.*
6.	1/23/04	**CASE 4089343: 15-month-old male with accidental ingestion** *American Association of Poison Control Centers reported 15-month-old male may have accidentally ingested his grandparent's rosiglitazone and or glyburide/metformin (Glucovance). The child had a seizure at home and his blood glucose was 11 mg/dL*

No.	FDA Rcvd Date	Case Description
		upon arrival at the emergency room. Dextrose solution was administered. The next day, the child's blood glucose was ~80 mg/dL and the child was discharged.
7.	1/23/04	**CASE 4070184: 2-year-old male with accidental ingestion** *American Association of Poison Control Centers reported choking and cough in a 2-year-old male who may have ingested a tablet found on the floor at his grandmother's house. The grandmother takes rosiglitazone, benazepril (Lotensin) and carisprodol (Soma). The child "cried excessively and fell asleep in the car on the way home." No outcome reported.*
8.	10/6/03	**CASE 4003323: 5-year-old female with accidental ingestion** *Physician reports a 5-year-old female took two 4-mg rosiglitazone tablets belonging to her grandmother. The child was observed at the hospital for less than 24 hours, showed no evidence of hypoglycemia, and was discharged without sequelae.*
9.	7/3/03	**CASE: 3923489: Male twin A exposed to rosiglitazone in utero** *Attorney reports male twin A, who was born three months premature (gestational age ~29 weeks) developed fatal liver failure, congestive heart failure, and other medical problems. The mother was 26-years-of-age with a history of "inability to conceive" and was prescribed clomiphene and metformin. Due to unspecified intolerance, metformin was switched to rosiglitazone 4 mg daily. The in utero exposure time to rosiglitazone was about 5 weeks.* *The twins were born on ——— In July, twin B improved; however, twin A "started to show an enlarged liver." A liver biopsy was performed but results were inconclusive. "The problem list included: respiratory distress syndrome, sepsis, hypotension, chronic lung disease, direct hyperbilirubinemia, urinary tract infection, coagulopathy, narcotic dependence, renal calculi, liver failure, biliary atresia, jejunal obstruction, portal hypertension and suspected esophageal varices, anemia, hyperaldosteronemia, malabsorption and failure to thrive with ileostomy, hypophosphatemia, hyponatremia, hypercalcemia, hypochloremia, hyperkalemia, hypoalbuminemia, hypercarbia, fluid retention, GI bleeding, neutropenia, thrombocytopenia, bacteremia, and pneumonia." On October 12, 2001, the following medical conditions were also noted: growth failure, cholestatic hepatopathy with fibrosis, cirrhosis and liver failure. "Physical examination revealed severe jaundice with icteric sclera, intermittent systolic cardiac murmur along the left sternal border, intermittent tachypnea, very distended abdomen with prominent veins, hepatopsplenomegaly, and scrotal and penile edema." The child died on ———— from "respiratory failure secondary to ascites from liver failure"*
10.	7/3/03	**CASE: 3923490: Male twin B exposed to rosiglitazone in utero** *Attorney reports male twin B who was born three months premature (gestation age ~29 weeks) and developed cholestatic liver disease and multiple other medical conditions was exposed in utero to rosiglitazone for about 5 weeks. The mother was 26-years-of-age with history of "inability to conceive" but no history of diabetes. The mother was prescribed clomiphene and metformin but due to unspecified intolerance, metformin was switched to rosiglitazone 4 mg daily. Twin B was born on ———— , and following a "prolonged and stressful hospital course," was discharged from the hospital on ———— Outpatient follow up the next day indicated Twin B had " scars on his abdomen from ileostomy and takedown," "persistent high bilirubins, seizures, gastroesophageal reflux, a history of perforated bowel secondary to necrotizing entercolitis which required surgery and retinopathy of prematurity." The pediatrician also later noted, "continued bronzed hyperbilirubinemia jaundiced appearance due to some cholestatic liver disease, liver failure or liver problems, right-sided hydrocele, a larger left-sided hydrocele without hernia, distended abdomen, umbilical hernia, and possible left-sided inguinal hernia."*

No.	FDA Rcvd Date	Case Description
		The patient was seen by another pediatric practice from about September 28 2001 to at least March 4, 2003, during which time the "physician noted: cholestasis, respiratory distress syndrome, abdominal perforation, "BPD", mild developmental delay appropriate for degree of prematurity, poor weight gain around 18 months of age, upper respiratory infection, circumcision, incarcerated left inguinal hernia (reduced twice) with subsequent herniorrhaphy, and gastroenteritis with vomiting and diarrhea."
11.	6/12/03	**CASE 3955750: Male twins exposed to rosiglitazone in utero** *A United Kingdom physician reports the occurrence of fetal stress and premature birth of twins born to a 40-year-old female with a history of polycystic ovarian syndrome and morbid obesity who was taking rosiglitazone (8 mg daily, start date unknown), acarbose, metformin, felodipine, perindopril, atorvastatin, salbutamol, beclomethasone and dextropropoxyphene/acetaminophen. The gestational age at birth was 32 weeks plus six days. Rosiglitazone was discontinued one month before the day of delivery of the twins.*
12.	12/27/01	**CASE 3751264: 16-year-old female experienced elevated LFTs** *A physician reported a 16-year-old obese (weight: 420 pounds) female on rosiglitazone (for unspecified indication) experienced liver function tests (LFTs) three times the normal limit. Rosigilitazone was discontinued and the LFTs returned to normal. Concurrent medications and medical conditions not specified.*
13.	3/23/01	**CASE 3657770: 6-month-old female with breast tissue development (in utero exposure)** *Mother reported she took rosiglitazone during the first trimester (for about 3 weeks) and at her daughter's 6-month check up, the physician found left breast tissue developing and elevated hormones: estradiol 24 pg/mL (reference <8 pg/mL), testosterone 13 ng/dL (reference <10 ng/dL), cortisol 17.5 mcg/dL (reference 6-23 mcg/dL), FSH 5.5 IU/L (reference 0-2 IU/L), LH 0.1 IU/L (reference 0-1 IU/L). There were no complications during delivery. Outcome not reported.*
14.	2/28/01	**CASE 3616428: 11-year-old male with hepatomegaly and elevated LFTs** *Physician reports 11-year-old male with history of obesity, type 2 diabetes, hypogonadism, bilateral slipping of capital femoral epiphysis, and headaches. The child had normal ALT (17) and AST (23) in 1997. On [redacted] the child started rosiglitazone 2 mg daily. On [redacted] ALT was elevated at 63, AST 37 (normal range 0-37) and GGT 34 (normal range 11-51). ALT on [redacted] was 109, AST was elevated at 44, and GGT was still within normal limits. The child had no jaundice or hepatomegaly. Rosiglitazone was discontinued.* *[redacted], ALT was 179, AST 76, and GGT 57. January 16, the child complained of decreased appetite, mild fatigue and upper respiratory symptoms. Exam did not reveal fever, jaundice or hepatomegaly. Laboratory tests showed ALT 240, AST 85, GGT 82, triglycerides 297, bilirubin normal. Hepatitis A Ab, Hepatitis B core antibody. Hepatitis B sAg, Hepatitis C Ab and monospot were all negative. Laboratory testing [redacted] showed ALT 208, AST 85, and GGT 88. The remaining liver function studies, including PT and PTT, were all negative. Epstein Barr virus antibody panel showed EBV IgG was positive at 7.77 index value, EBV nuclear antigen positive at 9.83 index value, and EBV IgM antibody negative. Abdominal ultrasound on [redacted] showed hepatomegaly with fatty infiltration.* *On [redacted] ALT was 189, AST 78, and GGT 72. As of [redacted] the patient had not yet recovered. However ALT was decreasing.*

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/s/

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3/10/2006 02:56:01 PM
DRUG SAFETY OFFICE REVIEWER

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