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Subject:	Update: Acute Liver Failure
Drug Name(s):	Avandia® (rosiglitazone) and Actos® (pioglitazone)
Application Type/Number:	NDA 021-071 and NDA 021-073
Applicant/sponsor:	SB Pharmco and Takeda Pharms NA
OSE RCM #:	2008-1790

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1 INTRODUCTION

This review provides an updated analysis of acute liver failure reports, submitted to the Adverse Events Reporting System (AERS) database, associated with the use of rosiglitazone (Avandia®) or pioglitazone (Actos®). As requested by the Division of Metabolism and Endocrinology Products (DMEP), this review will serve as part of the **documentation for DMEP's response to a citiz**en petition (CP) submitted to the Food and Drug Administration (FDA) on October 30, 2008.[1]

1.1 BACKGROUND

On October 30, 2008, the Public Citizen's Health Research Group (Public Citizen) **submitted a CP to the FDA "to immediately ban the diabetes drug, Avandia® (rosiglitazone; GlaxoSmithKline)".**[1] The request for removal of Avandia® is based on multiple, serious risks including liver failure. In addition, the CP states that from 1997 to **2006, "14 cases of liver failure, of which 12 resulted in death", are associated with** rosiglitazone therapy.[1] DMEP provided copies of these 14 cases to DPVI to determine if they were captured in the AERS case series reviewed.

In April 2005, DPVI completed an AERS review of *fatal liver* and *transplant cases* associated with rosiglitazone and pioglitazone, from marketing in 1999 to April 1, 2005.[2] At that time, the review identified a total of 9 cases for Avandia®: 7 cases of fatal acute liver failure (ALF) and 2 cases of liver transplantation (1 alive and 1 wait-listed) and a total of 12 fatal ALF cases associated with Actos®.[2]

In addition, this review provided an epidemiological analysis of reporting rates (RepRs) for *fatal liver* and *transplant cases* associated with the use of rosiglitazone, pioglitazone, and troglitazone. Troglitazone (Rezulin® by Parke Davis Pharmaceutical) was approved in January 1997, as the first peroxisome proliferators-activated receptor gamma agonist (PPARγ), in the U.S. market. However, Rezulin® was subsequently withdrawn from the U.S. market, in March 2000, due to hepatotoxicity including liver failure.[2]

Using data from IMS Health, National Prescription Audit, the cumulative projected numbers of total prescriptions dispensed in the U.S. were [redacted] and [redacted] for Avandia® and Actos®, respectively, from marketing in 1999 to December 2004. The estimated RepRs for cases of *fatal liver failure* and *transplant* among the three PPARγ agonists were 63 cases per million person-years for Rezulin®, 3 cases for Avandia®, and 4 cases for Actos®.[2] The background rate of hospitalization for idiopathic ALF was estimated to be less than 1 per million person-years[3]. Although substantially lower than

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[1] Petition to Immediately Ban Diabetes Drug Rosiglitazone (AVANDIA) (HRG Publication #1848). Created on 10/29/2008. Available at: http://www.citizen.org/publications/index.cfm?sectionID=101&criteria=avandia&path_info=%2Fpublications%2Findex.cfm.

[2] Green L. Postmarketing Safety Review: Review of Fatal and Transplant Cases of Acute Liver Failure Associated with Avandia® (Rosiglitazone, NDA 21-071) and Actos® (Pioglitazone, NDA 21-073), PID #: D040742. Dated: April 26, 2005. Available at: Division Files System, online. Accessed: December 2008.

[3] Graham DJ, et al. Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. Am J Gastroenterol 2003;98:175-179.

for troglitazone, the above estimated RepRs for Avandia® and Actos® are still above the estimated background rate.

2 MATERIAL REVIEWED

2.1 RELEVANT PRODUCT LABELING

See Appendix 1 and 2 below for product labeling that relates to hepatotoxicity for Avandia® (rosiglitazone maleate) and Actos® (pioglitazone hydrochloride) respectively.

2.2 AERS STRATEGY AND FINDINGS

For this updated review, the AERS search criteria and case selections were identical to those in the original 2005 review.[2] The AERS data time period for the original review was from the U.S. approval dates in 1999 for Avandia® (rosiglitazone) and Actos® (pioglitazone) to April 1, 2005.

For this updated review, the AERS data time period was April 2, 2005 through December 31, 2008.

2.2.1 AERS Search Criteria

The following MedDRA terms were used for the AERS search:

- **Hepatic Failure and Associated Disorders (HLT)**
- **Hepatic Fibrosis and Cirrhosis (HLT)**
- **Hepatic Necrosis (PT)**
- **Hepatitis Fulminant (PT)**
- **Liver Transplant (PT)**

2.2.2 Case Selection Criteria

Cases of ALF were selected if they had:

- **A clinical diagnosis of ALF in the absence of other causes of liver necrosis:**
  - Acute hepatic insult, e.g., shock or sepsis
  - Un-confounded evidence for chronic liver disease, e.g., cirrhosis
  - Evidence for current infection with Hepatitis A, B, or C, or other viruses
  - Other primary drugs associated with liver necrosis
- **An onset of symptoms, if present, temporally related to drug therapy**
- **A** *fatal* outcome or *liver transplantation* (fatal or non-fatal outcome)
- **A domestic reporting origin**

2.2.3 Adjudication of Reports Cited in Citizen Petition

Fourteen AERS reports were cited in the CP as part of their documentation to provide evidence of the hepatotoxic effects of Avandia®. The CP states that the reports were

submitted to the FDA between 1997 and 2006. Each Individual Surveillance Report (ISR) was assessed from the criteria established by the original 2005 review. Elements considered were AERS time period, search criteria, case selection criteria, and reporters' geographic location.

After this assessment, and based on the Case Selection Criteria outlined in section 2.2.2, DPVI determined the following:

- 9 reports were excluded from the original 2005 review because they did not meet the case definition
- 4 reports were identified and included in the original 2005 review

This adjudication left one Avandia® case remaining from the 14 cases cited in the CP; this case was submitted to AERS in January 2005. This case was not previously captured by the original 2005 review because it was not available in the active database at the time the AERS search was performed. It was not captured for this updated review because it is outside of the AERS search time period, which is April 2, 2005 through December 31, 2008.

However, this case does meet the case selection criteria outlined above in section 2.2.2 and will be included in section **2.4 EPIDEMIOLOGICAL ANALYSIS**. See Appendix 3 for the listing of ISR reports cited in CP and case deposition with respect to the original 2005 review, and Appendix 4 for narrative of Avandia® case identified in the adjudication process of section 2.2.3.

2.2.4 AERS Findings

AERS was searched for each drug using the search criteria outlined above in section 2.2.1. These searches resulted in the respective *crude* number of reports for each drug: 11 pioglitazone, and 24 rosiglitazone. The search results were further narrowed to identify: 1) a report of liver failure with an outcome of death, and 2) a report of liver transplantation, with a fatal or non-fatal outcome. This narrowing process resulted in the following number of fatal or liver transplant cases by drug: 5 pioglitazone and 9 rosiglitazone.

After performing a hands-on review of each individual case and applying the case selection criteria in section 2.2.2, cases for each drug were eliminated for the reasons listed in Table 1. This resulted in the following number of unduplicated cases for each drug: pioglitazone 1 and rosiglitazone 1.

The demographic and clinical characteristics of the case associated with each drug are shown in Table 2.

Table 1: Cases Excluded from AERS Series of Fatal ALF or Liver Transplant Cases associated with Pioglitazone and Rosiglitazone AERS Search Period: April 2, 2005 through December 31, 2008		
Reason for Exclusion, # of Cases	**Pioglitazone, N=5**	**Rosiglitazone, N=9**
Did not meet case definition	4	7
Duplicate report	NA	1
Remaining Cases	1	1

NA - not applicable

Note: the Avandia® case (ISR #: 4546487) identified in section **2.2.3 Adjudication of Reports Cited in CP** was included in the cumulative RepRs calculated for 1999 through December 2008. See section **2.4.2.2 Prescription-Time-Based RepR** for RepR estimates based on the inclusion of this case.

Table 2: Demographic and Clinical Characteristics of U.S. *Fatal ALF* and *Liver Transplants* Cases associated with Pioglitazone (N=1) and Rosiglitazone (N=1) AERS Search Period: April 2, 2005 through December 31, 2008						
	Age (years)	Dose (mg/day)	Time to Event (days)	Total Bilirubin (mg/dL)	ALT (IU/L)	AST (IU/L)
Pioglitazone (N=1)						
Values	62	45	NA	NA	NA	NA
Gender	Male					
Biopsy	**Yes – findings were consistent** with drug-induced liver toxicity; liver failure					
Autopsy	NA					
Transplant	NA					
FDA Receipt Year	2007					
Event Year	2007					
Rosiglitazone (N=1)						
Values	NA	NA	60 days approximately	NA	NA	NA
Gender	Female					
Biopsy	NA					
Autopsy	NA					
Transplant	**"Patient was hospitalized and awaiting liver transplant."**					
FDA Receipt Year	2005					
Event Year	NA					

NA - not applicable

After the case adjudication process, the majority of the excluded cases did not provided sufficient clinical data to document ALF. They are either consumer (8) or attorney (2) reports; one case was not diagnosed as liver failure. In reports submitted by healthcare professionals, the reporting quality is poor. Attempts to follow-up with the reporters of the two identified cases were made, but neither reporter provided any additional information.

Case Narratives:

Pioglitazone - ISR # 5321021: (*Fatal Liver Failure*)

A 62-year-old male, began taking pioglitazone 45 mg (dosing regimen not provided) on Dec. 26, 2006, due to uncontrolled blood sugars. In May 2005, the patient was taking rosiglitazone (dose, regimen, and length of therapy not provided) which was stopped due to edema; insulin was continued. On Dec. 16, 2006, his relevant baseline levels were ALT 33, AST 36, and bilirubin 1.0 (units of measure and normal values were not provided). On an unreported date, he was hospitalized and diagnosed with *elevated liver function tests* (LFTs) and *liver damage*. On an unreported date, the patient underwent a *liver biopsy with findings that were consistent with drug-induced liver toxicity and liver failure*. The *patient died in March 2007* (exact date not reported). His past medical history included type II diabetes mellitus since 2001, hepatitis, unspecified lung damage and a subsequent lung transplant in 2004, hypertension, and hyperlipidemia. Concomitant medications included: furosemide, prednisone, pantoprazole, tacrolimus, atorvastatin, and insulin glargine.

Rosiglitazone - ISR # 640258: (*Liver Transplant*)

A female (age not provided), treated with rosiglitazone for approximately 2 months (dose and dates of administration not provided), was hospitalized and diagnosed with *liver failure* and *jaundice*. At the time of report, the patient **was "*hospitalized and awaiting liver transplant*." Rosiglitazone was** discontinued (date not provided). No information was provided regarding concomitant medications or past medical history.

2.3 DRUG UTILIZATION

2.3.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ (see Appendix 5) was used to determine the various retail and non-retail channels of distribution for Avandia® and Actos® (data not provided).[4] According to IMS Health, IMS National Sales **Perspectives™, the retail setting (chain stores, independent stores, and food stores)** accounted for nearly 70% of Avandia® sales and 84% of Actos® sales for year 2008.

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[4] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 2-12-2009, File: 0902ava.dvr.

Mail order pharmacies accounted for 20% and 8% of Avandia® and Actos® sales, respectively.

2.3.2 Data Sources used

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. Outpatient prescription use was derived from SDI, Vector One®: National (VONA) database. We examined nationally projected estimates of Avandia® prescriptions dispensed by retail pharmacies from April 2005 to year 2008 and the average number of days of therapy dispensed per prescription. We examined the projected number of patients who filled a prescription for Avandia® at a U.S. retail pharmacy using SDI, Total Patient Tracker (TPT) from April 2005 to year 2008. Database descriptions can be found in the Appendix 5. Actos®, Actoplus Met®, Avandamet®, Avandaryl®, and Duetact® were used as comparators.

2.3.3 Drug Utilization Data Results

2.3.4 Projected Number of U.S. Retail Dispensed Prescriptions and Projected Number of Patient Filling U.S. Retail Dispensed Prescriptions

2.3.4.1 Avandia® and rosiglitazone combination products

In year 2008, 3.1 million Avandia® prescriptions were dispensed to 594,781 patients. Dispensed Avandia® prescriptions decreased by 57% (from 7.1 million prescriptions) and patient counts decreased by 61% (from 1.5 million patients) from year 2007 to 2008. Rosiglitazone combination products, Avandamet and Avandaryl, dispensed prescriptions decreased by 34% (from 1.7 million to 1.1 million prescriptions) and nearly 40% (from 524,830 to 315,392 prescriptions), respectively, from year 2007 to 2008. Avandamet and Avandaryl patient counts decreased by 40% (from 377,439 to 228,121 patients) and 46.5% (from 116,671 to 62,405 patients), respectively, from year 2007 to 2008 (see Tables 1 and 2 in Appendix 6).

2.3.4.2 Actos® and pioglitazone combination products

In year 2008, 12.5 million Actos® prescriptions were dispensed to 2.30 million patients. Dispensed Actos® prescriptions increased by around 2% (from around 12.3 million prescriptions) and patient counts decreased by around 2% (from around 2.34 million patients) from year 2007 to 2008. Pioglitazone combination products, Actoplus Met® and Duetact®, dispensed prescriptions increased by 18% (from 1.3 million to 1.6 million prescriptions) and 76.7% (from 73,745 to 130,328 prescriptions), respectively, from year 2007 to 2008. Actoplus Met® and Duetact®, patients counts increased by 8% (from 304,346 to 328,332 patients) and 28% (from 23,495 to 29,994 patients), respectively, from year 2007 to 2008 (see Tables 1 and 2 in Appendix 6).

2.3.5 The Number of Days of Therapy Dispensed

Table 1 in Appendix 6 provides projected dispensed prescriptions and the average number of days of therapy per prescription dispensed to the consumer for each product (i.e. days supply). Each of these products are, on average, dispensed with 33 days supply of medication.

2.3.6 Drug Utilization Findings

Drug utilization findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that Avandia® and Actos® were distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. SDI's TPT and VONA provide estimates of patient counts and the number of prescriptions dispensed through outpatient retail pharmacies in the United States, respectively. Mail order data was not provided and thus, retail dispensed prescriptions may be underestimated. However, over the past few years (2007 to 2008), an estimated 60% decrease in Avandia® dispensed prescriptions and patients counts occurred. Comparatively, Actos® utilization had been relatively steady.

2.4 EPIDEMIOLOGICAL ANALYSIS

2.4.1 Methods

To put ALF adverse events associated with Avandia® and Actos® into context, we estimated RepRs. The RepRs were defined as the number of fatal liver or transplant cases reported to AERS divided by total number of patients exposed or prescriptions dispensed nationwide during the same time period.

We estimated RepRs for ALF cases associated with Avandia® and Actos® and compared them with population background rates. We also compared RepRs for Avandia® or Actos® across different time periods, April 2005-2008 versus 1999-2005. RepRs for both drugs were also estimated from their marketing in 1999 to December 31, 2008. Combination products, Actoplus Met®, Avandamet®, Avandaryl®, and Duetact® were not used for estimating RepRs.

RepRs were estimated for Avandia® and Actos® based on two different methods. One method was the Patient-Based method and the other was the Prescription-Time-Based method. These methods are adapted from the draft document entitled "Data source and methods for calculating drug adverse event RepRs: An evaluation of current practices" by the Reporting Rate Working Group from DEPI/OSE.

<u>Patient-Based method</u>

The numerator was the raw count of fatal liver failure or transplant cases reported to AERS associated with Avandia® or Actos® reported during April 2005- December 2008. The denominator was total number of nationally projected patients exposed to Avandia® or Actos® for the same time period (see equation 1). Data for the denominator were derived from SDI, Total Patient Tracker (TPT).

Equation 1: Patient-based RepR formula

$$Patient-based\ RepR = \frac{Total\ Number\ of\ Liver\ Failure\ Cases}{Total\ Patients\ Exposed}$$

Prescription-Time-Based method

The numerator was the raw count of fatal liver failure or transplant cases reported to AERS associated with Avandia® or Actos®, from April 2005 to 2008. For the denominator, we used total number of prescriptions dispensed nationally (#Rx) for the same time period and the mean number of days of drug therapy. These data were used to estimate the total number of therapy days, which was then divided by 365.25 days to obtain person-years of exposure (see equation 2). Data for the denominator derived from SDI, Vector One®: National (VONA) database.

Equation 2: Prescription-Time-Based RepR formula

$$Prescription-time-based\ RepR = \frac{Total\ Number\ of\ Liver\ Failure\ Cases}{\#\ Rx^{*}\ Mean\ Days\ of\ Therapy/365.25}$$

2.4.2 Results of Reporting Rates

A total of two cases of ALF were reported in AERS from 04/01/2005 to 12/31/2008 associated with either Avandia® or Actos®. One transplant case associated with Avandia®, the other fatal liver failure case associated with Actos®.

2.4.2.1 Patient-Based RepR

The estimated RepRs were based on the crude count of ALF cases in AERS and the total number of U.S nationally projected Avandia® and Actos® users. The estimated RepRs are 0.3 and 0.2 cases per million persons for Avandia® and Actos®, respectively, from April 1, 2005 to December 31, 2008 (Table 3 below).

Table 3: Reporting rates for liver failure cases associated with Avandia® and Actos® from April 2005- December 2008, using the Patient-Based method.

	April 2005-December 2008		
Drug	**Total # of Patients***	**Total # of cases**	**RepR****
Avandia®	3,381,687	1	0.30
Actos®	4,567,426	1	0.22

* Data extracted from SDI, Total Patient Tracker (TPT) on 2-12-09.
**Numbers are per million persons

2.4.2.2 Prescription-Time-Based RepR

The estimated RepRs were based on the crude count of ALF cases in AERS and the total days/365.25 of U.S. nationally projected Avandia® and Actos® prescribed. The estimated RepRs are approximately 0.4 and 0.3 cases per million person-years for Avandia® and Actos®, from April 1, 2005 to December 31, 2008 (Table 4 below).

Table 4: Reporting rates for liver failure cases associated with Avandia® and Actos® from April 2005 to December 2008, using the Prescription-Time-Based method.

	April 2005-December 2008		
Drug	Total Days of Drug Exposure*	Total # of cases	RepR**
Avandia®	978,922,129	1	0.37
Actos®	1,456,439,064	1	0.25

* Calculated as the product of number of prescriptions dispensed nationally and the mean number of days of drug therapy (Appendix 6, Table 1.). Data extracted from SDI Vector One®: National (VONA) on 2-12-09.
** Numbers are per million person-years

From section **2.2.3 Adjudication of Reports Cited in CP**, a case not previously captured in the original 2005 review was identified for Avandia®. Therefore, the total numbers of ALF cases are 10 and 12 associated with Avandia® and Actos®, respectively, from marketing in 1999 to April 1, 2005. The estimated RepRs are approximately 3 and 4 cases per million person-years for Avandia® and Actos®, from marketing in 1999 to April 1, 2005 (table not shown). The cumulative ALF cases are 11 and 13 associated with Avandia® and Actos®, respectively, from marketing in 1999 to December 31, 2008. Using Prescription-Time-Based method, the estimated RepRs are approximately 2 cases per million person-years for both Avandia® and Actos®, from January 1, 1999 to December 31, 2008 (table not shown).

2.4.3 Interpretation of Reporting Rates

In this report, we provide two methods for RepRs calculation. Many factors are to be considered when estimating the RepRs, including the purpose of the RepR comparison, the type of adverse event of the case reports, and the drug use patterns. We used the Patient-Based RepR, a proportion-based method, as it is preferred for chronically used drugs that are associated with short latency adverse event. The Prescription-Time-Based method is a rate-based method that is preferable for long-term drug use and can generate a measure comparable to the background rate, i.e., person-years of drug exposure.

The estimated background rate of hospitalization for idiopathic ALF is less than 1 per million person-years.[3] A preliminary assessment of the signal of ALF suggests that RepRs for Avandia® and Actos® are similar during the period from April 2005 to 2008 (0.4 and 0.3 cases per million person-years, respectively) and are not higher than the estimated background rate. A further comparison of the RepRs between the two time periods, suggests that the RepRs from April 2005 to 2008 are not higher than those from 1999 to March 2005 for both Avandia® and Actos®. The RepRs for Avandia® and

Actos® are 3 and 4 cases per million person-years from 1999 to March 31, 2005 respectively. There might be a couple of reasons why the liver failure RepRs were higher for the period 1999-March 2005. The surge in liver failure reports during years 1999-2005 might be stimulated by the market withdrawal of troglitazone, a drug of the same class, in March 2000 due to liver toxicity. Also, during that time period, cases of liver toxicity were encouraged to be reported. After 2005, the decrease in reporting frequency for severe liver toxicity might have been due to the fact that the drugs have been on the market for several years.[5,6] Overall, the estimated RepRs are 2 cases per million person-years for both Avandia® and Actos®, from marketing in 1999 to December 31, 2008.

There are several limitations regarding the RepRs estimation methods. For the numerator estimate, AERS may underestimate the adverse events due to under-reporting. For the denominator, we used prescriptions for Avandia® or Actos® as a proxy for drug exposure while it is possible that not all dispensed prescriptions were used. Due to these limitations, even though we used two methods for RepR estimation, the results should be interpreted with caution. The RepRs cannot be interpreted as true incidence rates within the population.

We conclude that a potential association between Avandia® and Actos® with liver toxicity cannot be ruled out. The estimated RepRs during 1999-2005 was higher than the background rate suggesting a positive association between Avandia® and Actos® and liver toxicity. We expected to have more cases reported during 1999-2005 as compared to the following time period 2005-2008, because adverse events reporting known to be higher during the first few years after the drug has been introduced into the market. Moreover, because of the passive nature of the spontaneous reporting system and underreporting of adverse events in AERS, the observed RepRs for these drugs may be underestimated. Therefore, even though RepRs for the second period (2005- 2008) were not higher than the estimated background rate, we cannot exclude the potential association between Avandia® or Actos® and liver failure.

3 DISCUSSION

Idiosyncratic drug hepatotoxicity is the most frequent cause for a drug not to be approved or to be withdrawn from the market.[7,8,9] Drug-induced liver injuries (DILI) are caused by different mechanisms. Although most significant hepatotoxins cause predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from

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[5] McAdams MA, Governale LA, Swartz L, Hammad TA, Dal Pan GJ. Identifying patterns of adverse event reporting for four members of the angiotensin II receptor blockers class of drugs: revisiting the Weber effect. Pharmacoepidemiol Drug Saf. 2008 Sep;17(9):882-9.

[6] Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, eds, Advances in Information Research, Vol. 6. New York: Raven, 1984; pp 1-7.

[7] Kaplowitz N. Rules and laws of drug hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):231-3.

[8] Premarketing Evaluation of Drug-Induced Liver Injury - Concept Paper. [Draft]. FDA / CDER and CBER. Prepared by the Hepatotoxicity Working Group. January 2007.

[9] Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 Apr;15(4):241-3.

injured liver cells without prominent evidence of hepatobiliary obstruction, the pattern of injury can vary.[10]

The injuries can resemble almost all known liver diseases and there are no diagnostic findings, even upon liver biopsy, that make diagnosis of DILI certain.[11] Therefore, as described by Lee and Senior, the diagnosis of DILI is one of exclusion; one in which sufficient clinical information must be gathered to rule out other possible causes of the abnormal findings seen.[11] To make a diagnosis of DILI requires collecting certain clinical data at the time of the acute situation. Since this is not often done, the information that is available is usually inadequate to establish the likelihood of drug causality with any reasonable degree of confidence.[11]

The AERS database is FDA's voluntary reporting system and as a result, report documentation may be of poor quality or incomplete. Other limitations of AERS include the subjectivity of adverse event recognition, and the lack of denominator data.[12] But the system strengths include the generation of signals for potential safety concerns for further investigation, and the detection of rare adverse events that are acute and severe in nature.[12]

The estimated background rate for hospitalization due to idiopathic ALF is less than 1 per million person-years.[3] The estimated RepRs for *fatal ALF* and *transplantation* cases from the original 2005 review were 3 cases- for Avandia® and 4 cases per million person-years for Actos®. The estimated RepRs are 2 cases per million person-years for both Avandia® and Actos®, from marketing in 1999 to December 31, 2008. Therefore, based on this updated AERS review, we observed a similar pattern of liver injury associated with the use of Actos® and Avandia® as noted in the original 2005 review. At the present time, OSE does not recommend labeling changes regarding liver injury.

[10] FDA / CDER Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation [*Draft Guidance*]. Posted October 2007. Available at: http://www.fda.gov/cder/guidance/7507dft.htm. Accessed: March 2009.
[11] Lee WM and Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. Toxicol Pathol. 2005;33(1):155-64.
[12] U.S. Food and Drug Administration. MedWatch-The FDA Medical Products Reporting Program. The Clinical Impact of Adverse Event Reporting. Posted October 1996. Available at: http://www.fda.gov/medwatch/articles/medcont/medcont.htm. Accessed on March 2009.

APPENDIX 1

Relevant Product Labeling for Avandia® (rosiglitazone maleate) and Medication Guide

Avandia®

HIGHLIGHTS OF PRESCRIBING INFORMATION

DOSAGE AND ADMINISTRATION

Do not initiate AVANDIA if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels. (2.4)

FULL PRESCRIBING INFORMATION CONTENTS*

2 DOSAGE AND ADMINISTRATION
2.4 Specific Patient Populations

5 WARNINGS AND PRECAUTIONS
5.6 Hepatic Effects

6 ADVERSE REACTIONS
6.2 Laboratory Abnormalities
6.3 Postmarketing Experience

2 DOSAGE AND ADMINISTRATION

2.4 Specific Patient Populations

Hepatic Impairment: Liver enzymes should be measured prior to initiating treatment with AVANDIA. Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). After initiation of AVANDIA, liver enzymes should be monitored periodically per the clinical judgment of the healthcare professional. *[See Warnings and Precautions (5.6) and Clinical Pharmacology (12.3).]*

5 WARNINGS AND PRECAUTIONS

5.6 Hepatic Effects

Liver enzymes should be measured prior to the initiation of therapy with AVANDIA in all patients and periodically thereafter per the clinical judgment of the healthcare professional. Therapy with AVANDIA should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5X upper limit of normal). Patients with mildly elevated liver enzymes (ALT levels •2.5X upper limit of normal) at baseline or during therapy with AVANDIA should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with

Appendix 1, continued:

AVANDIA in patients with mild liver enzyme elevations should proceed with caution and include close clinical follow-up, including liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen. If at any time ALT levels increase to >3X the upper limit of normal in patients on therapy with AVANDIA, liver enzyme levels should be rechecked as soon as possible. If ALT levels remain >3X the upper limit of normal, therapy with AVANDIA should be discontinued.

If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with AVANDIA should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued. *[See Adverse Reactions (6.2, 6.3).]*

6 ADVERSE REACTIONS

6.2 Laboratory Abnormalities

Serum Transaminase Levels: In pre-approval clinical studies in 4,598 patients treated with AVANDIA (3,600 patient-years of exposure) and in a long-term 4- to 6-year study in 1,456 patients treated with AVANDIA (4,954 patient-years exposure), there was no evidence of drug-induced hepatotoxicity.

In pre-approval controlled trials, 0.2% of patients treated with AVANDIA had elevations in ALT >3X the upper limit of normal compared to 0.2% on placebo and 0.5% on active comparators. The ALT elevations in patients treated with AVANDIA were reversible. Hyperbilirubinemia was found in 0.3% of patients treated with AVANDIA compared with 0.9% treated with placebo and 1% in patients treated with active comparators. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure. *[See Warnings and Precautions (5.6).]*

In the 4- to 6-year ADOPT trial, patients treated with AVANDIA (4,954 patient-years exposure), glyburide (4,244 patient-years exposure), or metformin (4,906 patient-years exposure), as monotherapy, had the same rate of ALT increase to >3X upper limit of normal (0.3 per 100 patient-years exposure).

6.3 Postmarketing Experience

There are postmarketing reports with AVANDIA of hepatitis, hepatic enzyme elevations to 3 or more times the upper limit of normal, and hepatic failure with and without fatal outcome, although causality has not been established.

Appendix 1, continued:

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Special Populations:

Hepatic Impairment: Unbound oral clearance of rosiglitazone was significantly lower in patients with moderate to severe liver disease (Child-Pugh Class B/C) compared to healthy subjects. As a result, unbound Cmax and AUC0-inf were increased 2- and 3-fold, respectively. Elimination half-life for rosiglitazone was about 2 hours longer in patients with liver disease, compared to healthy subjects.

Therapy with AVANDIA should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline *[see Warnings and Precautions (5.6)]*.

17 PATIENT COUNSELING INFORMATION

17.1 Patient Advice

Patients should be informed of the following:

- Blood will be drawn to check their liver function prior to the start of therapy and periodically thereafter per the clinical judgment of the healthcare professional.
  Patients with unexplained symptoms of nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine should immediately report these symptoms to their physician.

Appendix 1, continued:

MEDICATION GUIDE
AVANDIA® (ah-VAN-dee-a)
rosiglitazone maleate tablets

What should I tell my doctor before taking AVANDIA?
Before taking AVANDIA, tell your doctor about all your medical conditions, including if you:

- **have liver problems.** Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed.
- **had liver problems while taking REZULIN® (troglitazone), another medicine for diabetes.**

How should I take AVANDIA?

- Your doctor should do blood tests to check your liver before you start AVANDIA and during treatment as needed. Your doctor should also do regular blood sugar tests (for example, "A1C") to monitor your response to AVANDIA.

What are possible side effects of AVANDIA? AVANDIA may cause serious side effects including:

- **Liver problems.** It is important for your liver to be working normally when you take AVANDIA. Your doctor should do blood tests to check your liver before you start taking AVANDIA and during treatment as needed. Call your doctor right away if you have unexplained symptoms such as:
    - nausea or vomiting
    - stomach pain
    - unusual or unexplained tiredness
    - loss of appetite
    - dark urine
    - yellowing of your skin or the whites of your eyes.

APPENDIX 2

Relevant Product Labeling for Actos® (pioglitazone hydrochloride)

ACTOS®

CLINICAL PHARMACOLOGY

Special Populations

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see **PRECAUTIONS**, Hepatic Effects).

PRECAUTIONS

General

Hepatic Effects: In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values • 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Appendix 2, continued:

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

Laboratory Tests
FPG and HbA1c measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see **PRECAUTIONS, General,** Hepatic Effects and **ADVERSE REACTIONS, Serum Transaminase Levels**).

Information for Patients
Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

ADVERSE REACTIONS
Laboratory Abnormalities
Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values • 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials

Appendix 2, continued:

in the U.S. due to abnormal liver function tests. In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS**, **General**, Hepatic Effects).

DOSAGE AND ADMINISTRATION
Maximum Recommended Dose
Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see **PRECAUTIONS**, **General**, Hepatic Effects and **CLINICAL PHARMACOLOGY**, **Special Populations**, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see **PRECAUTIONS**, **General**, Hepatic Effects).

APPENDIX 3

Listing of Individual Surveillance Reports Cited in Citizen Petition

ISR #	FDA Received Year	Sex	Age	Reported Outcomes	Location	Report Disposition with respect to Original 2005 Review
3719979	2001	M	64	DE, HO	F	Foreign - United Kingdom and did not meet the case definition
3916550	2002	F	71	DE, HO	F	Foreign - Netherlands and did not meet the case definition
5786217	2008	M	52	DE, HO, LT	F	Foreign - Saudi Arabia and did not meet the case definition
4546487	2005	M	70	DE, LT, HO, DS, OT	D	Not previously captured in original 2005 or updated review. Case is described in this review, see section 2.2.4
3478562	2000	F	46	DE, HO, LT	D	Identified and included in original 2005 review
3842674	2001	M	82	DE	D	Identified and included in original 2005 review
3862007	2002	M	48	DE, HO, RI, OT	D	Identified and included in original 2005 review
4123750	2003	M	70	DE, LT, HO, DS, OT	D	Identified and included in original 2005 review
3485085	2000	F	80	HO	D	Non-fatal outcome; did not meet the case definition, not included in original 2005 review
3895241	2002	M	60	LT	D	Non-fatal outcome; did not meet the case definition, not included in original 2005 review
4237854	2003	F	60	HO, RI	D	Non-fatal outcome; did not meet the case definition, not included in original 2005 review
4587193	2005	F	57	HO, OT	D	Non-fatal outcome; did not meet the case definition, not included in original 2005 review
4520331	2004	M	72	DE	D	Previously identified but excluded, did not meet the case definition
4605945	2005	M	73	DE, HO, OT	D	Previously identified but excluded, did not meet the case definition

APPENDIX 4

Narrative of Case identified in the Adjudication Process of section 2.2.3

Rosiglitazone - ISR # 4546487: (*Fatal Liver Failure*)

A 70-year-old male, was initiated on rosiglitazone 4 mg daily, on March 20, 2004. Twelve days after starting rosiglitazone maleate, on April 1, 2004, the patient experienced acute liver failure, elevated liver enzymes, jaundice and elevated bilirubin level. He was hospitalized on [redacted]; rosiglitazone was discontinued the same day. The patient laboratory were ALT 440, bilirubin 30.4, international normalization ratio (INR) 1.4, hepatitis and autoimmune serologies all negative, diagnostic imaging tests showed gallstones, and biliary dilatation was negative. A liver biopsy performed on [redacted], showed acute necrosis and negative cirrhosis consistent with drug effect. On an unreported date later in 2004, the patient was again hospitalized with worsening jaundice. He had severe hypoalbuminemia, evidence of a marked decrease in liver synthetic function, and a prolonged INR which could not be corrected with vitamin K. Allopurinol and gabapentin were discontinued, and he was started on dialysis. Another liver biopsy was performed on October 4th, showing marked cholestasis, markedly less lobular and interstitial hepatitis, focal atrophy of hepatocyte plates and portal venular dilatation when compared to prior biopsy in April 2004. The patient became progressively more encephalopathic; dialysis was stopped, and the patient in hospice care where he died on [redacted]. His concurrent medical conditions included chronic renal failure, chronic thrombocytopenia, focal segmental glomerulosclerosis, urinary tract infection, hypersplenism, and hypertension. Concurrent medications included metoprolol, losartan, iron sulfate, allopurinol, furosemide, and epoetin alfa.

APPENDIX 5
Database descriptions

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI, LLC: Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the U.S. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

APPENDIX 6
Tables

Table 1

Projected Number of U.S. Retail Dispensed Prescriptions, April 2005 through December 2008

	4/2005-12/2005	2006	2007	2008	4/2005-12/2008	4/2005-12/2008
	TRxs	TRxs	TRxs	TRxs	TRxs	Mean Days Therapy
TOTAL MARKET	16,785,331	24,733,882	23,072,508	18,759,652	83,351,373	33.0
Actos	7,461,118	11,329,039	12,297,891	12,517,912	43,605,960	33.4
Avandia	8,193,469	11,331,164	7,126,837	3,103,002	29,754,472	32.9
Actoplus Met	20,483	782,923	1,331,629	1,566,732	3,701,767	32.2
Avandamet	1,110,261	917,004	1,717,576	1,126,286	4,871,127	31.9
Avandaryl	--	370,262	524,830	315,392	1,210,484	31.8
Duetact	--	3,490	73,745	130,328	207,563	32.2

SDI: Vector One®: National (VONA) Data extracted 2-12-2009.

File: 2008-1790 VONA 2-12-09 avandia actos Trx Therapy days April05to2008.qry

Table 2

Projected Number of Patients Who Filled a Prescriptions at a U.S. Retail Pharmacy, April 2005 to December 2008

Product	April to December 2005	2006	2007	2008	Grand Total April 2005 to December 2008
	Projected Patient Count	Projected Patient Count	Projected Patient Count	Projected Patient Count	Projected Patient Count
Grand Total	**3,648,478**	**4,470,083**	**4,214,380**	**3,403,576**	**7,988,834**
Actos	1,657,230	2,116,898	2,338,668	2,301,549	4,567,426
Avandia	1,858,628	2,120,410	1,533,767	594,781	3,381,687
Avandamet	458,437	345,503	377,439	228,121	902,904
Actoplus Met	16,702	218,671	304,346	328,332	556,765
Avandaryl	N/A	112,638	116,671	62,405	187,801
Duetact	N/A	2,767	23,495	29,994	43,386

SDI, Total Patient Tracker, data extracted 2-12-09. Source Files: TPT 2008-1790 avandia actos patients APR2005-2008.xls

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/s/

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