

PARKE DAVIS SUBMISSION

Troglitazone
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EMDAC BRIEFING DOCUMENT

TABLE OF CONTENTS

	Page
1. INTRODUCTION.....	4
1.1. Background: Pharmacology and Regulatory History	4
1.2. Safety and Efficacy Overview	5
1.3. The March 26, 1999 Advisory Committee Meeting.....	6
2. ADVERSE LIVER EVENTS ASSOCIATED WITH REZULIN.....	7
2.1. Adverse Liver Events in the Clinical Trials.....	8
2.2. Pathophysiology and Histology	9
2.2.1. Clinical Features	9
2.2.2. Histology.....	10
2.3. The Postmarketing Data.....	11
2.3:1. Patient Exposure: Overview	11
2.3.2. Postmarketing Reports of Liver-Related Death and Transplant.....	11
2.3.2.1. Complexity of Case Analysis	12
2.4. Estimated Incidence of Liver Failure.....	13
2.4.1. Clinical Trials	14
2.4.2. Postmarketing Liver Failure	15
2.4.3. Postmarketing Jaundice Reports.....	18
2.5. Intensity of Case Reporting.....	20
2.6. Conclusions as to Incidence and Liver Enzyme Monitoring	22
3. RISKS ASSOCIATED WITH DIABETES AND ITS TREATMENT	23
3.1. Risk of Liver Disease in Diabetes.....	23
3.2. Comparative Risks Associated With Other Antidiabetic Therapies	24
3.2.1. Risks Associated With Metformin	25
3.2.1.1. Clinical Trials.....	25
3.2.1.2. Postmarketing Reports	26
3.2.2. Risks Associated With Sulfonylureas.....	26
3.2.3. Risks Associated With Acarbose.....	28
3.2.4. Risks Associated With Insulin Therapy	28
3.2.5. Conclusions as to Comparative Risk	29

TABLE OF CONTENTS

	Page
4. THE BENEFITS OF REZULIN THERAPY	29
4.1. Nonglycemic Effects of Rezulin	32
5. THE BENEFIT-RISK ASSESSMENT OF REZULIN THERAPY	36
5.1. Risks Associated With Uncontrolled Diabetes	36
5.2. Long-Term Failure of Other Therapies.....	37
5.3. Clinical Trial Data: Efficacy and Sustained Effect of Rezulin	38
5.4. The Benefits of Rezulin Outweigh Associated Risks	39
6. REFERENCES.....	40

1. INTRODUCTION

On March 26, 1999, the Endocrinologic and Metabolic Drugs Advisory Committee will review efficacy and safety data relating to Rezulin® (troglitazone) tablets. In particular, the Advisory Committee will review postmarketing reports of adverse liver events, efficacy data relating to the 3 current approved indications for Rezulin, and data supporting a pending supplement for combination therapy with metformin and sulfonylureas. The data will show that the benefits of Rezulin in its current and proposed indications outweigh associated risks of adverse liver events. This submission provides a brief summary of some of the data that will be presented in detail at the March 26 meeting.

1.1. Background: Pharmacology and Regulatory History

Rezulin is the first of a new class of oral antidiabetic agents (the thiazolidinediones) that treats insulin resistance, which is a principal underlying cause of type 2 diabetes. In the presence of endogenous or exogenous insulin, Rezulin decreases gluconeogenesis, glucose output, and triglyceride synthesis in the liver, while increasing glucose uptake and utilization in skeletal muscle. Rezulin also increases glucose uptake and decreases fatty acid output in adipose tissue.

The initial indication for Rezulin as combination therapy with insulin was first reviewed by the Advisory Committee in December 1996. That indication was approved by the US Food and Drug Administration ("FDA") in January 1997. A supplemental application for use of Rezulin as either monotherapy or in combination with sulfonylureas was approved in August 1997. Rezulin also has been reviewed and approved by regulatory authorities in 14 other countries, see Appendix 1.

Troglitazone
Tablets

1.2. Safety and Efficacy Overview

Rezulin is an important addition to the limited armamentarium of therapies available to treat type 2 diabetes. In particular, the drug addresses an unmet medical need in the many patients who cannot achieve or sustain long-term glycemic control on other therapies. The drug's unique mechanism of action (PPAR₄ agonist) results in the direct reduction of insulin resistance in target tissues. The reduction in insulin resistance produced by Rezulin leads to reductions in plasma insulin and significant improvements in glycemic control. These effects are thought to reduce the risk of developing many of the more serious long-term complications of type 2 diabetes. Whether used as initial therapy after failure of diet and exercise or in combination with other agents such as metformin and/or sulfonylureas, Rezulin is associated with significant decreases in HbA_{1c} levels, enabling many patients to meet American Diabetes Association treatment goals for the first time. When used in combination with insulin, Rezulin significantly reduces or eliminates the need for exogenous insulin.

Based largely on the significant benefits of Rezulin therapy, the drug is well accepted by the medical community. Since market introduction in March 1997, Rezulin has been prescribed for approximately 1.6 million patients in the United States. Approximately 750,000 patients currently are being treated with the drug and approximately 560,000 patients have been treated in Japan.

With respect to overall safety, Rezulin is generally well-tolerated by most patients. Day-to-day tolerability is comparable to placebo and the drug does not cause hyperglycemia when used alone.

Rezulin has been associated with adverse liver events which, in rare cases, have led to transplant or death. As described in the initial product labeling, elevations in serum alanine aminotransferase (ALT) levels and 2 cases of jaundice were reported during the original clinical trials which provided the basis for the New Drug Application (NDA). Each of these patients normalized without permanent clinical complications, including

Troglitazone
Tablets

patients who continued on the drug despite the ALT elevations and the 2 jaundiced patients. No liver failures or liver-related deaths occurred during the clinical trials that preceded approval of the NDA.

After receipt of 2 postmarketing reports of liver failure, Parke-Davis initiated discussions with the FDA. After consultation with expert hepatologists and the FDA, Parke-Davis incorporated liver enzyme monitoring requirements in the product labeling in October 1997. Modifications to the monitoring requirements were made in December 1997 and July 1998 after continued analysis of the postmarketing data by Parke-Davis and the FDA. Attached as Appendix 2 is a summary of the key labeling changes relating to liver enzyme monitoring. The Company also issued "Dear Healthcare Professional" letters and initiated physician and patient education programs designed to assure awareness of the importance of liver enzyme monitoring.

As is discussed in more detail below, the actions taken by Parke-Davis and the FDA since October 1997 have been associated with a dramatic decrease in the incidence of serious adverse liver events. For example, the incidence of liver failure leading to death or transplant was approximately 1 in 37,000 during the first 11 months on the market (3/97-2/98) and approximately 1 in 104,000 during the second 11 months (3/98-3/99) on the market.

1.3. The March 26, 1999 Advisory Committee Meeting

As noted above, this document will provide a brief summary of the Rezulin safety and efficacy data. Parke-Davis will present a more comprehensive review of the data at the March 26, 1999 Advisory Committee meeting. In particular, the data presented in this document and at the March 26 meeting will focus on the following key points:

1. Rezulin is associated with rare, idiosyncratic adverse liver events leading to transplant or death (see Sections 2.1 and 2.3.2);

Troglitazone
Tablets

2. The incidence of adverse liver events leading to transplant or death is low and is comparable to the rates of fatal adverse events associated with other antidiabetic therapies (see Sections 2.4 and 3.2);
3. The incidence of Rezulin-associated adverse liver events has declined substantially since liver enzyme monitoring requirements were included in the product labeling (see Section 2.4);
4. The benefits of Rezulin in its current indications and in the pending indication for combination therapy with sulfonylureas and metformin are important and unique, and address an unmet medical need in patients poorly controlled on other therapies (see Section 4); and
5. The benefits of Rezulin clearly outweigh the rare risk of adverse liver events, and the benefit-risk profile of the drug has improved further as a result of labeling changes, patient and physician education initiatives, and communications to physicians initiated by Parke-Davis in agreement with FDA (see Section 5).

Rezulin has been the subject of significant media attention, and many reports have inaccurately described the facts regarding safety and other matters relating to the drug and to Parke-Davis. Parke-Davis welcomes this opportunity to review the facts regarding Rezulin in an objective, scientific forum, permitting a discussion that is in the best interests of the medical community and of patients with diabetes.

2. ADVERSE LIVER EVENTS ASSOCIATED WITH REZULIN

The focus of the safety discussion at the March 26, 1999 Advisory Committee meeting will be adverse liver events reported since March 1997, when Rezulin was first marketed. This Section will provide a brief overview of the clinical trial safety data and a detailed discussion of the postmarketing experience.

2.1. Adverse Liver Events in the Clinical Trials

During all clinical trials in North America preceding approval of the initial application, 475 patients were treated with placebo and 2510 patients were treated with Rezulin. Serum alanine aminotransferase (ALT) elevations $>3 \times \text{ULN}$ were observed in 48 (1.9%) Rezulin-treated patients and 3 (0.6%) placebo-treated patients. ALT elevations reflect the occurrence of hepatocellular change which may indicate actual or potential liver dysfunction.

Clinical protocols from these trials did not include rules for discontinuing therapy if liver enzyme elevations occurred. However, therapy was discontinued by the investigators for 20 of the 48 Rezulin-treated patients who had elevated ALT levels $>3 \times \text{ULN}$. Two of the 20 patients also developed reversible jaundice prior to discontinuation of therapy. The peak serum ALT exceeded $10 \times \text{ULN}$ in 12 patients and $30 \times \text{ULN}$ in 5 patients. Each of these patients, including the 2 jaundiced patients, normalized without any permanent clinical complications.

The onset of ALT elevations in the 20 patients who discontinued therapy due to ALT elevations was typically delayed; most peak ALT elevations occurred between 3 and 7 months of therapy (mean 147 days, median 124 days, standard deviation 86 days). One of these patients developed ALT $>3 \times \text{ULN}$ within 30 days of therapy initiation. Serum ALT levels promptly returned to baseline in most patients after therapy was discontinued (range 8 to 12 days, mean 55 days, standard deviation 34 days).

Twenty other Rezulin-treated patients who had ALT elevations $>3 \times \text{ULN}$ continued their therapy despite the laboratory findings. Five of those patients had serum ALT $>10 \times \text{ULN}$. Peak ALT elevations in these patients occurred between 2 and 18 months of therapy. Serum ALT levels returned to baseline and normalized in all of these patients without clinical manifestation despite continuation of therapy.

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The remaining 8 patients were found to have ALT elevations $>3 \times \text{ULN}$ at the end of study. Peak ALT elevations in these patients occurred between 2 and 9 months of therapy. Serum ALT levels returned to normal in each of these patients without clinical manifestation.

Based on the clinical data, the initial product labeling included the following precaution:

Hepatic: During all clinical studies in North America (N = 2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies consistent with an idiosyncratic drug reaction.

In addition, the initial labeling included the following language in the Adverse Reactions and Dosage and Administration sections.

Serum Transaminase Levels: During controlled clinical trials, 2.2% of Rezulin-treated patients had reversible elevations in aspartate aminotransferase (AST) or ALT $>3 \times \text{ULN}$, compared with 0.6% of patients receiving placebo. Hyperbilirubinemia ($>1.25 \times \text{ULN}$) was found in 0.7% of Rezulin-treated patients compared with 1.7% of patients receiving placebo. In the population of patients treated with Rezulin, mean and median values for bilirubin, AST, ALT, alkaline phosphatase (ALP), and γ -glutamyltransferase (GGT) were decreased at the final visit compared with baseline, while values for lactate dehydrogenase (LDH) were increased slightly.

Patients With Hepatic Impairment: Rezulin should be used with caution in patients with hepatic disease.

2.2. Pathophysiology and Histology

2.2.1. Clinical Features

The adverse liver events associated with Rezulin are typically hepatocellular. As a result, the early course of the event is characterized by elevations in serum ALT and AST (ALT generally higher than AST) without significant elevations in serum bilirubin or alkaline phosphatase. If the event becomes severe, alkaline phosphatase and bilirubin may rise. A

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rise in ALT levels may reflect hepatocellular change but does not always result in clinical manifestation if it is identified early. As noted above 19 patients with elevated ALT levels normalized despite continuation of therapy with Rezulin.

In the clinical trials, ALT elevations were generally asymptomatic. However, postmarketing reports of severe liver events have included symptoms characteristic of viral hepatitis, including malaise, anorexia, and occasionally abdominal pain. Fever was not observed in the clinical trials, but has been a feature of a few of the spontaneous reports. Rash and peripheral eosinophilia have not been a feature of Rezulin liver events.

The available data does not permit conclusions as to possible risk factors for Rezulin liver events (e.g., age, gender, dose, body size, concomitant medications).

2.2.2. Histology

Abstracted pathology reports from 20 patients and 4 published case reports from these 20 patients have been reviewed. Some of the variability in the findings listed below may be due to differences in the time intervals between illness and liver biopsy.

Of the 20 reports, 4 had no details on the histologic findings in the biopsy reports. These reports used general terms such as acute hepatitis (2), drug-induced hepatitis (1), and necroinflammatory changes (1). Of the remaining 16 cases, 15 describe bridging necrosis or collapse, 8 of which were severe enough to be termed submassive hepatic necrosis. Two of these cases stated that very little inflammation was seen, while 8 described chronic inflammatory cells in portal tracts. In 5 cases, eosinophils were noted in the pathology reports, while 4 reports described plasma cells, and 3 specifically mentioned lymphocytes. Eleven cases had cholestatic changes typified by neocholangiolar proliferation and cannicular bile plugs. Three reports described bile duct damage. Only one report describes fatty change. Seven reports mentioned the presence of fibrosis, one of which was cirrhotic.

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The overall impression from these 20 patients is that of active hepatitis with bridging necrosis, neocholangiolar proliferation and mixed portal infiltrates of eosinophils, plasma cells, and lymphocytes. The majority of these pathologic changes are non-specific, as is often seen in fulminant hepatitis regardless of etiology (virus, drug, or toxin). The presence of eosinophils is perhaps the only specific marker of a possible drug reaction.

Pertinent negative findings include the lack of fatty change (even though the target population is at an increased risk of steatohepatitis) and the lack of any zonal pattern to the necrosis.

2.3. The Postmarketing Data

2.3.1. Patient Exposure: Overview

Since market introduction in March 1997, Rezulin has been prescribed to approximately 1.6 million patients in the United States. Approximately 750,000 patients currently take the drug. See Appendix 3 for information on how patient exposure data are calculated.

2.3.2. Postmarketing Reports of Liver-Related Death and Transplant

The majority of reported adverse liver events have involved reversible elevations of ALT with no significant clinical complications. However, a small subset of patients has experienced liver failure leading to transplant or death. These cases will be the principal focus of the March 26, 1999 Advisory Committee meeting.

As of March 5, 1999, Parke-Davis has received 70 reports of deaths in the United States involving some mention of the liver, regardless of the relationship of the drug to the liver event or the outcome.

The FDA has classified 35 of these reports as "possibly" or "probably" related to the drug. Thirty-three were from spontaneous postmarketing reports and 2 were from

Troglitazone
Tablets

postmarketing clinical trials. Twenty-six of these reports involve a liver-related death and 9 involve a liver transplant (2 of whom died).

The FDA also has classified events involving 8 patients with encephalopathy, but who did not progress to liver failure or death, as possibly or probably related to Rezulin. Attached as Appendix 4 is a summary of the medical facts relating to the 35 death/transplant reports and the 8 encephalopathy reports.

In an effort to better understand the etiology of these events, Parke-Davis has referred all reports of adverse liver events to Dr. Paul Watkins, an expert hepatologist at the University of Michigan. Dr. Watkins will discuss the pathophysiology of these events at the March 26 Advisory Committee meeting.

In addition to the above-noted reports, 9 liver-related deaths have been reported in Japan, where the drug has been used by approximately 560,000 patients. Parke-Davis has not received any reports of liver transplant or liver-related death from other countries in which the drug is marketed.

2.3.2.1. Complexity of Case Analysis

Each of the reports of liver failure associated with Rezulin involves a complex set of facts which makes conclusive attribution of cause difficult if not impossible. As reflected in the following table, 38 of the 43 US cases of death, transplant, or encephalopathy involve patients who had complex medical histories, including one or more potential confounding factors that has been associated with some degree of liver dysfunction, such as hepatitis, liver necrosis, cirrhosis, jaundice, cholestatic jaundice, and elevated liver enzymes.

Table 1. Concurrent Medical Conditions (US)

Medical Condition	No. of Patients	Case Numbers ^a
Hypotension/shocked liver	1	30
History of alcohol abuse	4	11, 24, 28, 39
Sepsis	8	5, 7, 10, 15, 19, 22, 31, 33
Viral hepatitis or cytomegalovirus	10	1, 2, 5, 7, 18, 23, 24, 30, 34, 39
Autoimmune disease	10	3, 10, 11, 13, 17, 20, 22, 31, 35, 36
History of cardiac disease	12	8, 10, 15, 16, 25, 29, 30, 32, 35, 37, 41, 43
Pre-existing disease of liver, gallbladder, or biliary tract	12	1, 2, 4, 5, 7, 10, 11, 17, 23, 24, 29, 35
Concomitant or co-suspect medication	30	1, 4, 5, 8, 9, 11, 12, 13, 15, 16, 20, 21, 22, 23, 24, 25, 28, 29, 30, 31, 32, 34, 35, 36, 38, 39, 40, 41, 42, 43

^a The case numbers refer to the order of case discussion in Appendix 4.

In addition, these reports do not reflect on the effect of the liver enzyme monitoring recommendations because most of the cases involve patients who were not monitored according to the current product labeling. For example, of the 35 patients who progressed to liver failure or death:

- Eight of the events occurred prior to initiation of liver enzyme monitoring;
- Twenty-five of the 27 remaining death and transplant patients apparently were not monitored according to the recommendations in the product labeling; and
- Only 1 of the 35 death and transplant cases involved a patient who was monitored substantially in accordance with the product labeling as it exists today. See Appendix 4, case number 28.

2.4. Estimated Incidence of Liver Failure

As with any other drug, an estimate of the incidence of adverse liver events associated with Rezulin is complex and inexact. Several possible epidemiologic models can be created to evaluate the data from different perspectives.

The following analysis demonstrates that the incidence of liver failure in Rezulin-treated patients is low, and that liver enzyme monitoring requirements in the product labeling have further lowered the incidence. Section 3.2 will provide a comparative risk -

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assessment to show that the incidence of adverse events associated with Rezulin is comparable to the incidence of serious adverse events associated with other antidiabetic therapies.

2.4.1. Clinical Trials

As of March 1999, approximately 15,600 patients have taken Rezulin during the course of controlled clinical studies (Table 2). Table 3 shows the total number of liver-related deaths and transplants during the course of all studies that have been conducted to date. Because jaundice occurs prior to fulminant drug-induced liver failure (although approximately 90% of jaundice cases do not lead to death), the table also notes the incidence of jaundice during the clinical trials.

Table 2. Number of Patients in Controlled Clinical Trials Exposed to Rezulin Worldwide as of 02/01/99

	Completed Studies		Ongoing Studies	
	Number Enrolled	Exposure (Patient-Years)	Estimated Number Enrolled	Estimated Exposure (Patient-Years)
Parke-Davis				
Phase 2-3	2754	2264	301	47
Phase 4	1284	530	3317	1267
Glaxo Wellcome	3034	1227	169	89
Sankyo				
Phase 2-3	1539	558	--	--
Phase 4	1608	370	1000	460
NIH			585	
Total	10,219	4949	5372	1863

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Table 3. Number of Patients With Serious or Symptomatic Hepatic Events in Controlled Clinical Trials^a

	Number Exposed	Deaths	Nonfatal Events	
			Jaundice	Hospitalization
Parke-Davis				
Phase 2-3	3055		2	1
Phase 4	4601	1 ^b	1	1
Glaxo Wellcome	3203	0	0	0
Sankyo	4147	0	0	0
NIH	585	1 ^b	1	1
Total	15591	2 (0.01%)	4 (0.03%)	3 (0.02%)

^a Includes completed and ongoing studies

^b Patient experienced hospitalization, jaundice, and death.

Based on the data in Table 3, the incidence of liver failure leading to transplant or death in clinical studies is 2 in 15,591 Rezulin-treated patients or 1 in 7,800. This rate is much higher than the rate of reported events during the postmarketing experience (see Section 2.4.2), but it is not necessarily predictive of the actual postmarketing incidence for several reasons. First, based on the number of patients in the clinical trials and the applicable 95% confidence intervals, the clinical rate may be extrapolated to a rate anywhere between 1 in 3,000 and 1 in 64,000. Second, hepatologists generally expect a minimum of 10 or more jaundice cases to every liver drug-associated death. Only 4 jaundice cases occurred in the clinical studies, when a minimum of 20 cases would have been expected in relation to the 2 reported deaths. In contrast, the expected 10 to 1 jaundice/death ratio is generally reflected in the postmarketing experience (see Section 2.4.3). Third, the cases are complex and difficult to assess, making definitive attribution of causality and extrapolation of the data to the postmarketing experience somewhat speculative. The 2 reports of death are described in Appendix 4 patient numbers 18 and 28.

2.4.2. Postmarketing Liver Failure

In addition to the clinical data, estimates of incidence may be derived from available postmarketing data. The FDA has classified 35 postmarketing reports (including the

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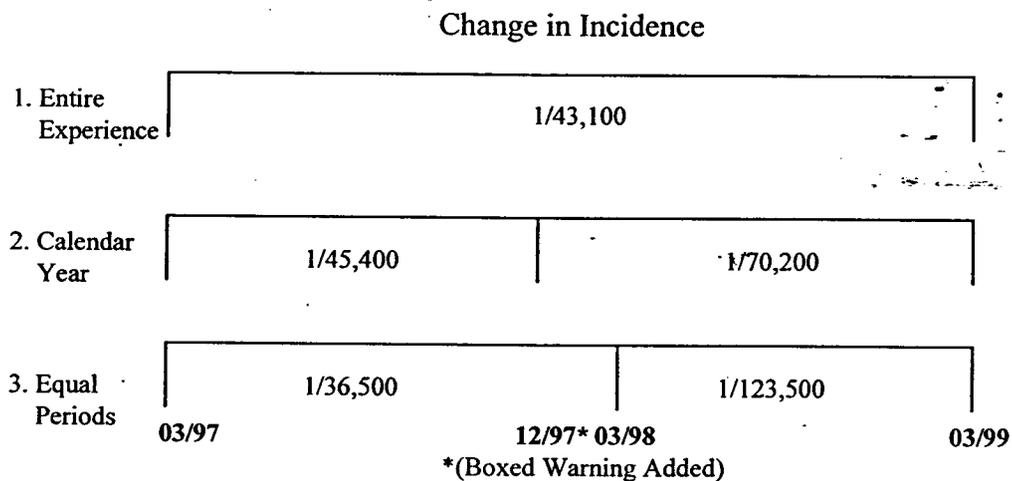
2 clinical trial cases) of liver-related death or transplant as possibly or probably drug-related. The crude rate is then 35 out of 1.6 million people exposed to drug. Although attribution of cause is subject to differing medical judgment, the following discussion is based on the FDA's analysis of the cases.

Based on the above-noted patient events, Parke-Davis has estimated the incidence of adverse liver events over several distinct timeframes:

1. the entire postmarketing experience (March 1997 through February 1999);
2. the first calendar year of marketing leading to incorporation of a boxed warning in the product labeling (March 1997 through December 1997) compared to the period following the boxed warning (January 1998 through February 1999); and
3. the first 11 months of marketing (March 1997 through February 1998) compared to the second 11 months of marketing (March 1998 through February 1999).

Troglitazone
Tablets

The number of events for each timeframe includes all reports of liver failure leading to transplant or death occurring during that timeframe. The population includes all patients exposed to the drug during that timeframe. Based on this analysis, the following chart shows that the incidence of reported serious adverse liver events has declined dramatically subsequent to changes in labeling requiring more extensive monitoring of liver function.



Incidence of Adverse Liver Events Over Time

Finally, it should be noted that the incidence of reported liver-related death and transplant since July 1998 (the period covered by the current labeling) is approximately 1 in 204,000. Because this period only covers 7 months, the rate may not reflect actual incidence. However, it is fair to conclude from current data and the table presented above that:

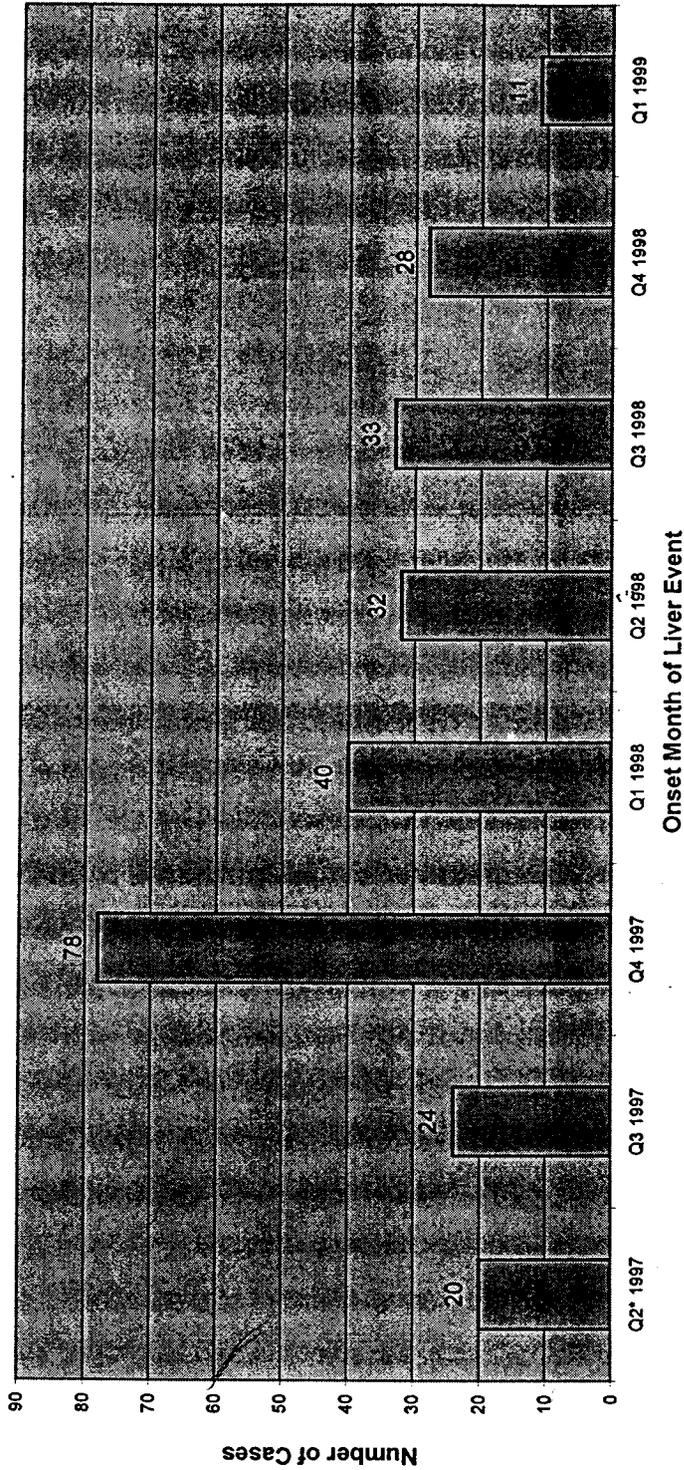
- the incidence of adverse liver events leading to death or transplant is low; and
- the incidence has decreased since liver enzyme monitoring recommendations were placed in the product labeling.

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2.4.3. Postmarketing Jaundice Reports

As noted above, each patient who progressed to liver failure initially presented with jaundice. Confirming what is generally predicted by expert hepatologists, there have been approximately 10 reports of jaundice for each reported death: 278 jaundice cases and 28 deaths. Moreover, Figure 1 confirms that the number of jaundice or bilirubinemia cases over time has declined subsequent to the implementation of liver enzyme monitoring recommendations despite an increased patient population exposed to the drug.

Jaundice and Bilirubinemia Cases by Date of Onset as of March 05, 1999 By Quarter N=266



* Q2 1997 includes March 1997 data.
As of March 5, 1999, 278 cases are classified as Jaundice and Bilirubinemia cases.
12 cases have missing onset month.

266 cases are displayed.

Figure 1

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Overall, the number reports of jaundice cases fell by approximately 54% during 1998 as compared to 1997. The number of jaundice cases peaked in the fourth quarter of 1997 (73 reports of onset during the quarter). The average number of jaundice cases occurring in each quarter of 1998 was 27. Parke-Davis has received reports of 9 cases of jaundice occurring in January 1999 and 2 cases in February 1999. The decline in jaundice cases is particularly significant because jaundice is a necessary precursor to liver failure (although the majority of jaundice cases do not progress to liver failure).

2.5. Intensity of Case Reporting

Estimates of incidence may be affected depending on the level of reporting of the events in question. Although there may be some underreporting of adverse events, the following facts support the conclusion that the level of reporting is high for liver-related deaths and transplants relating to Rezulin.

First, several epidemiological studies have confirmed that publicity--particularly adverse publicity--increases or stimulates reporting of adverse events.^{1,2} In those studies, publicity in lay or scientific media increased reporting by 50% to 100%.³ Rezulin clearly has been the subject of an enormous amount of adverse (and inaccurate) publicity. For example, since December 1996, there have been more than 285 million media impressions related to Rezulin (print and broadcast, based on audience reached analysts) that were negative in content.

Moreover, Parke-Davis' efforts to inform physicians and patients regarding these events have been extensive. Since October 1997, Parke-Davis has issued three "Dear Healthcare Professional" letters and 1 statgram regarding adverse liver events. Each of these letters reached approximately 500,000 physicians, pharmacists, and diabetes educators.

Parke-Davis maintains an extensive, well-informed sales force and a medical liaison group which communicate relevant safety information to healthcare professionals. The Company also has implemented a nationwide patient and physician communication

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program which includes information about these events. All of these efforts are likely to further increase the level of reporting of these adverse events.

Second, several studies have demonstrated that the level of reporting of more severe adverse events is significantly higher than it is for less serious events. This may be particularly true for organ damage.⁴⁻⁹ It therefore is likely that the level of reporting is high with respect to liver events involving jaundice or liver failure.

Third, many studies have demonstrated that the level of adverse event reporting is highest during the first 2 to 3 years that a drug is on the market.^{4,8,10,11} Rezulin has been on the market for 2 years.

Fourth, physicians are more likely to report an unexpected or idiosyncratic reaction than one that is well-known to be related to the pharmacological properties of a drug.¹² The hepatic events reported in association with Rezulin are idiosyncratic and therefore likely to generate reports at a higher rate than events involving expected pharmacological drug reactions.

Fifth, there is a clear trend to increased reporting in recent years, particularly since the advent of the MedWatch system and in relation to new drugs and severe adverse events.^{5,10,6,13,14}

In summary, although it is not possible to estimate the exact level of reporting of liver-related deaths and transplants associated with Rezulin, the reporting rate is likely to be high, based on the factors described above. In an effort to test this conclusion, Parke-Davis requested 2 separate surveys of liver transplant centers in the United States. The intent of the studies was to determine whether all transplants involving liver failure possibly relating to Rezulin had been reported. The Acute Liver Failure Database, which compiles data from 11 transplant centers in the United States, was searched for Rezulin and/or diabetes transplants. Of the 89 cases, 5 (5.6%) had diabetes (3 treated with Rezulin, 2 treated with diet). These 3 cases were the first of the 7 transplant cases

Troglitazone
Tablets

identified and reported to Parke-Davis and FDA. The database has no record of a liver transplant involving a patient taking Rezulin since that time. Additionally, a formal survey was conducted of the United Network for Organ Sharing (UNOS), which supplied information on transplants in patients with diabetes and/or on Rezulin. Of the 4,394 total liver transplants in 1998, 2 patients were known to be on Rezulin. Both of these cases had been reported to Parke-Davis and the FDA. As reporting of concomitant medications is not always accurate, an attempt was made to contact every liver transplant center in the United States and each was asked to supply the same information. Again, 2 transplant patients on Rezulin were identified. Both of these patients had been reported to Parke-Davis and FDA. These surveys provide strong support for the conclusion that there is a high level of reporting with respect to adverse liver events associated with Rezulin.

2.6. Conclusions as to Incidence and Liver Enzyme Monitoring

Rezulin is associated with rare cases of serious adverse liver events that have led to liver transplant or death in some patients. Since the implementation of liver enzyme monitoring, there has been a dramatic reduction in these rare events.

In addition to the decline in incidence, the importance of liver enzyme monitoring is illustrated by the fact that 34 of the 35 cases of transplant or death either involved a patient whose event onset predated the initiation of liver enzyme monitoring requirements, or a patient who was not monitored according to the then-current labeling at the time of onset.

Based on these data, the following conclusions may be made:

- Liver failure is a serious but rare idiosyncratic adverse event associated with Rezulin;
- The rate of liver failure has declined substantially since the product labeling was changed to incorporate liver enzyme monitoring; and
- Continuing physician and patient education regarding the importance of monitoring is warranted to improve compliance further.

3. RISKS ASSOCIATED WITH DIABETES AND ITS TREATMENT

The preceding Section characterized the risk of adverse liver events associated with Rezulin. In addition to risk quantification, it is important to evaluate the significance of that risk in relation to risks associated with the underlying disease and with other available therapies for diabetes.

3.1. Risk of Liver Disease in Diabetes

Many reports and studies suggest that diabetes is associated with an increased incidence of liver dysfunction, although the exact incidence and relationship of the disease to liver dysfunction is not completely understood. One report estimated that approximately 28% to 37% of diabetes patients have some form of liver dysfunction, and biopsy studies of persons with insulin resistant states have reported high rates of non-alcoholic steatohepatitis.¹⁵ Other studies have noted an increased incidence of, for example, hepatitis and hepatic coma, including a 4.2% rate of hepatitis C among diabetes patients as compared to 1.6% in a non-diabetic control group.¹⁶

The association of liver disease to diabetes was further investigated in a study sponsored by Glaxo Wellcome. Glaxo Wellcome commissioned the Boston Collaborative Drug Surveillance Program to study the frequency of liver disease in patients with diabetes who were treated with oral hypoglycemic drugs. In this study of 44,406 patients, 4,216 (9.5%) had a pre-existing condition linked to liver disease prior to receiving any study medication. Among these 4,216 patients, 21% had a history of liver disease, 36% had congestive heart failure, 29% had cancer, 3% had been diagnosed with alcoholism, and 12% had some combination of these conditions.¹⁷

Of the remaining 40,190 subjects, 605 (1.5%) were identified with a first-time diagnosis of liver disorder during exposure to an oral hypoglycemic agent, (none received Rezulin) 249 of whom developed a predisposing condition after receiving an oral hypoglycemic agent but before the diagnosis of liver disorder. One hundred eighty-six of the

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Tablets

605 patients developed mild asymptomatic liver enzyme abnormalities that were considered clinically relevant, and 113 subjects had a specified non-drug cause for the diagnosed liver disorder.

Of the 605 subjects identified with a first-time diagnosis of liver disorder, 57 exhibited symptoms consistent with possible drug-induced disorders, including 27 cases of jaundice and one patient who developed jaundice shortly after receiving metformin and glyburide and died 1 month later of liver failure.

The conclusion drawn from the study results is that the background rate of liver disease in a type 2 diabetic population is relatively high and should be considered when evaluating spontaneous reports of liver disease in diabetic patients taking oral hypoglycemic agents.¹⁷ It is important to note that troglitazone was not available in the United Kingdom at the time of the study.

3.2. Comparative Risks Associated With Other Antidiabetic Therapies

Rezulin and other antidiabetic drugs are indicated for the treatment of a chronic and potentially life-threatening disease. Pharmacotherapy is not optional for type 2 diabetes patients if diet and exercise fail to maintain blood glucose at acceptable levels, and all currently approved antidiabetic agents have been associated with reports of life-threatening and fatal adverse events. Because therapy is required, and therapeutic options are limited, it is helpful to evaluate these therapies in relation to each another. This Section provides a summary of comparative risk information relating to Rezulin and other available therapies for the treatment of type 2 diabetes. We will focus in particular on metformin because its therapeutic use by physicians is comparable to that for Rezulin, it was recently approved, and the risk of fatal lactic acidosis associated with metformin has been broadly studied and is well-characterized.

3.2.1. Risks Associated With Metformin

Metformin is a biguanide and is the most highly prescribed oral antidiabetic agent in the United States. It is believed to lower blood glucose by reducing glucose output by the liver without stimulating insulin secretion.¹⁸ The drug has been associated with lactic acidosis, a potentially lethal metabolic disorder characterized by low arterial pH (<7.35) and elevated arterial lactate levels (>5.0 mEq/L). Reported case fatality rates in patients with lactic acidosis range from 30% to 50%, regardless of intervention.¹⁸

3.2.1.1. Clinical Trials

An FDA review of the metformin NDA estimated that lactic acidosis occurred with an incidence of 1.76 cases per 1000 patient-years of exposure. No lactic acidosis deaths were reported during Phase 2 and 3 clinical studies. However, based on estimates derived from Phase 4 clinical trial data submitted with the metformin NDA, fatal lactic acidosis may occur at a rate of 0.88 per thousand patient-years.¹⁹

With respect to Rezulin, no liver-related deaths or transplants occurred during Phase 2 and 3 clinical studies. Based on the 2 liver-related deaths occurring during Phase 4 studies, the rate of fatal hepatic failure in Rezulin clinical trials was 0.29 per thousand patient-years. Thus, the comparative clinical trial experience is:

Metformin	0.88/1000 patient-years (fatal lactic acidosis)
Rezulin	0.29/1000 patient-years (fatal hepatic failure)

In addition to lactic acidosis, the labeling for metformin includes a warning that patients receiving therapy with a biguanide antidiabetic drug like metformin have a risk of cardiovascular mortality 2.5 times higher than patients treated with diet alone.

3.2.1.2. Postmarketing Reports

A comparative evaluation of the postmarketing experience for metformin and Rezulin shows that the rates of death from metformin-associated lactic acidosis and Rezulin-associated hepatic failure generally are comparable. In separate publications, FDA medical reviewers reported postmarketing data relating to the 2 drugs. From these publications, incidence estimates may be calculated.

The following table shows incidence estimated during the first 13 to 15 months of marketing for each therapy.

Table 4. Comparison of First Year Postmarketing Data for Metformin and Rezulin

	Dates	Fatal Reports Received	Exposure in Patients	Rate/100,000 Patients Exposed
Metformin ^a	May 1995-Jun 1996	20	~1 million	2.0
Rezulin ^b	Mar 1997-May 1998	17 ^c	1,050,885 ^c	1.7

^a Misbin R. et al (NEJM:1998)

^b Misbin R. (Annals of Int Med:1999)

^c Excludes patients from Japan.

Attached as Appendix 5 are references to additional sources for estimates of fatal lactic acidosis associated with metformin.

The postmarketing data thus confirm that the rate of fatal adverse liver events associated with Rezulin is no greater than the rate of fatal lactic acidosis associated with metformin using data reported in the same manner.

3.2.2. Risks Associated With Sulfonylureas

Sulfonylureas have been used to treat hyperglycemia associated with diabetes since the mid-1960s. They exert their antihyperglycemic effects largely by increasing the sensitivity of the pancreas to blood glucose, resulting in an increase in insulin secretion.

Troglitazone
Tablets

Because of their ability to increase insulin secretion, sulfonylureas have been associated with hypoglycemia, which may be a serious and potentially life-threatening event.

Sulfonylureas have also been associated with serious cardiovascular effects.

The association of sulfonylureas to hypoglycemia has been reported in extensive clinical trials. For example:

- In 21 clinical trials relating to glimepiride, the incidence of hypoglycemia ranged from 13.9% to 21.2%, and the incidence of hypoglycemia in the 2 comparator sulfonylureas (glyburide and glipizide) was 16.3% and 20.6%, respectively²⁰;
- In a 2-year prospective study of glibenclamide and chlorpropamide, the rate of hypoglycemia was 19 per 1,000 patient-years²¹; and
- In a 6-year, randomized, controlled clinical trial of more than 4,000 patients, the incidence of hypoglycemia was 170 cases per 1,000 patients, and the incidence of serious events requiring third-party assistance or hospitalization was 7 per 1,000 patients²².

In addition, the product labeling for all sulfonylureas includes a warning that the risk of cardiovascular mortality associated with the class is 2.5 times higher than in patients treated with diet alone.

Data from postmarketing experience with sulfonylureas also confirms the association of hypoglycemia to drugs in that class:

- Some studies suggest that severe hypoglycemia may occur at a rate of 0.19 to 0.24 cases per thousand patient-years, and may occur as often as 10 cases per 1,000 patient-years in elderly patients^{23,24}; and

Troglitazone
Tablets

- Mortality rates from hypoglycemia ranged in some studies from 0.014 to 0.033 deaths per 1,000 patient-years²⁴.

3.2.3. Risks Associated With Acarbose

Acarbose is an oral antidiabetic agent that inhibits the intestinal enzymes that break down complex carbohydrates into glucose. This inhibition results in a reduced uptake of glucose by the gastrointestinal tract, which in turn lowers blood glucose levels in diabetics.

The product labeling for acarbose in the United States reports "in approximately 3 million patient-years of international post-marketing experience with PRECOSE®, 62 cases of serum transaminase elevations >500 IU/L (29 of which were associated with jaundice) have been reported. Forty-one of these 62 patients received treatment with 100 mg t.i.d. or greater and 33 of 45 patients for whom weight was reported weighed <60 kg. In the 59 cases where follow-up was recorded, hepatic abnormalities improved or resolved upon discontinuation of PRECOSE® in 55 and were unchanged in two. Two patients in Japan died of fulminant hepatitis; the relationship to acarbose is unclear."

3.2.4. Risks Associated With Insulin Therapy

Fatal hypoglycemia associated with insulin use was previously perceived to be uncommon in type 2 diabetes. However, recent data from clinical trials and postmarketing reports suggest that hypoglycemia is a risk associated with insulin therapy:

- In a 6-year, randomized, controlled clinical trial of over 4,000 patients in the United Kingdom, the incidence of serious hypoglycemic events requiring third-party assistance or hospitalization was 23 per 1,000 patients²²;

Troglitazone
Tablets

- In 14 randomized, controlled trials of over 2,000 patients, the rate of severe hypoglycemia was 79 per 1,000 patient-years among intensive therapy patients, and 46 per 1,000 patient-years in conventional therapy groups²⁵;
- Other studies have reported an estimated range of hypoglycemia between 30 to 100 cases per 1,000 patient-years;^{21,23,26} and
- One report estimated that more than 90% of all insulin-treated patients experience one or more episodes of serious hypoglycemia, and between 3% to 7% experience fatal hypoglycemia.²⁷

3.2.5. Conclusions as to Comparative Risk

All of the therapies available to treat type 2 diabetes are relatively safe, but each has been associated with fatal adverse events. With respect to safety (risk), this Section confirms that the estimated incidence of adverse liver events associated with Rezulin is no greater than risks of fatal adverse events associated with other therapies for type 2 diabetes.

Moreover, safety must not be evaluated in a vacuum. Each drug must be considered in light of its risks and benefits, and the FDA has determined that the benefits of each of the available therapies outweigh associated risks. The following section describes the significant and unique benefits of Rezulin in its current indication and the proposed triple therapy combination for which an sNDA is under review.

4. THE BENEFITS OF REZULIN THERAPY

Rezulin improves glycemic control in patients with type 2 diabetes, either as monotherapy or in combination with other agents, as documented by clinically significant reductions in HbA_{1c} in 4 clinical trials (Figure 2). These studies were conducted in patients representing the spectrum of severity of diabetes, ranging from patients who

Troglitazone
Tablets

were uncontrolled on diet or half maximal sulfonylurea therapy in the monotherapy trial to patients who were uncontrolled on maximum doses of sulfonylurea, a combination of sulfonylurea and metformin, or >30 IU/day of insulin. Results confirm that:

- **Monotherapy.** Monotherapy with 600 mg/day of Rezulin reduced HbA_{1c} values by 1% compared with a 0.4% increase in patients treated with placebo (adjusted mean difference from placebo -1.4% HbA_{1c}; p <0.05) (Study 991-032);
- **Combination With Sulfonylureas.** Rezulin at 600 mg/day in combination with a sulfonylurea reduced HbA_{1c} values by 1.8% compared with an increase of 0.9% in patients treated with glyburide only (adjusted mean difference from placebo/glyburide -2.7% HbA_{1c}; p <0.0001) (Study 991-055);
- **Combination With Insulin.** Rezulin at 600 mg/day in combination with insulin reduced HbA_{1c} by 1.41% compared with a 0.12% reduction for patients treated with placebo (adjusted mean difference from placebo/Rezulin -1.29% HbA_{1c} with a 30 unit Rezulin dose reduction; p <0.0001) (Study 991-040); and
- **Combination With Metformin and Sulfonylureas.** A combination of Rezulin at 400 mg/day with metformin and a sulfonylurea reduced HbA_{1c} by 1.3% compared with an increase of 0.1% for patients treated with placebo and the metformin/sulfonylurea combination (Study 991-105).

Additive Efficacy of Rezulin

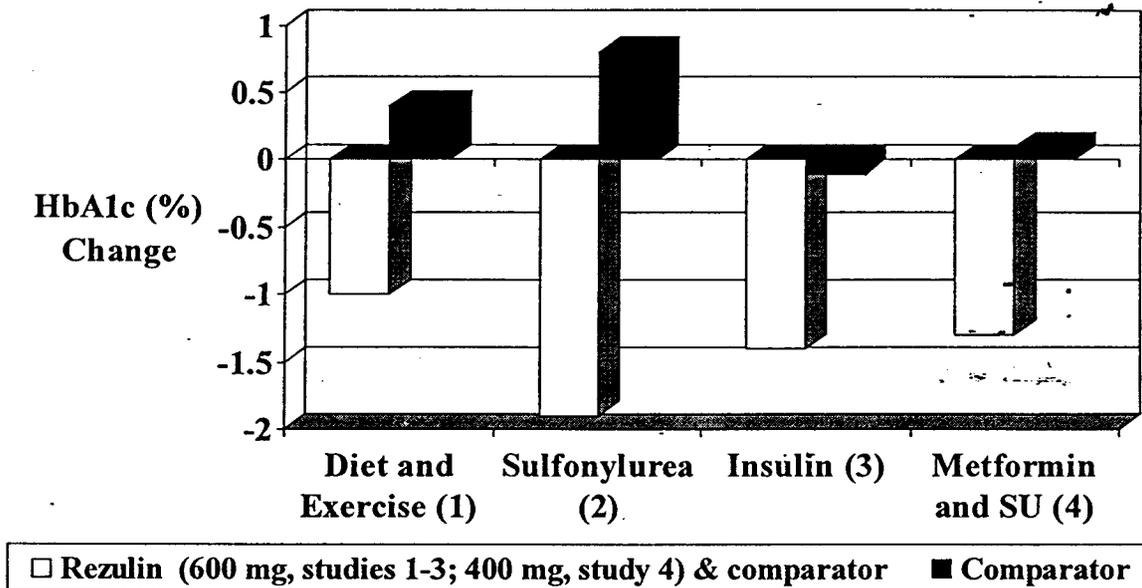


Figure 2. Adjusted Mean Change From Baseline in HbA_{1c}

The benefits of Rezulin therapy were also evident when data from these studies were summarized according to criteria defined by the ADA as suggesting additional pharmacological action (an HbA_{1c} >8%).

- Among patients receiving concomitant insulin, 30% of those treated with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1c} value ≤8% following 6 months of treatment, compared with 11% of placebo-treated patients (991-040);
- When Rezulin was administered in combination with glyburide, 33% of patients treated with the 400/12 mg and 60% of patients treated with the 600/12 mg Rezulin/glyburide dosage combinations achieved an HbA_{1c} ≤8%, compared with 10%

of patients treated with glyburide only for 52 weeks. After an additional 72 weeks of open-label treatment, 61% of patients who maintained the 400/12 mg combination and 69% of patients who maintained the 600/12 mg combination had HbA_{1c} values ≤8%; and

- In the monotherapy trial, 71% of the 47 patients who maintained the 600-mg/day Rezulin dose throughout the double-blind and open-label phases had an HbA_{1c} ≤8%.

Further, 62% of patients receiving long-term Rezulin monotherapy at the 600 mg/day dose achieved the ADA goal of HbA_{1c} ≤7%. Among patients treated with Rezulin in combination with glyburide, 29% who received the 400/12 mg combination and 51% who received the 600/12 mg combination achieved an HbA_{1c} ≤7%. These are significant achievements in the treatment of a disease in which complications account for 12% of US health care expenditures.²⁸⁻³³

A summary of the studies supporting approval of Rezulin for use as monotherapy and in combination with insulin or a sulfonylurea is presented in Table 5. Individual summaries of the studies included in the pending sNDA for the approval of Rezulin in combination with metformin are presented in Appendix 6.

4.1. Nonglycemic Effects of Rezulin

In addition to improving glycemic control, Rezulin appears to have beneficial effects on several cardiovascular risk factors which may be especially relevant in patients with type 2 diabetes mellitus, as well as other insulin-resistant states (e.g., impaired glucose tolerance, polycystic ovarian syndrome). While not yet definite or proven related to improved cardiovascular outcomes, taken together these effects are consistent with what would be expected from the drug's direct amelioration of insulin resistance. Clinical trial data and reports from the published literature regarding these effects are briefly reported here.

Troglitazone
Tablets

In clinical trials, Rezulin has been shown to reduce free fatty acid and triglyceride levels and to increase HDL levels as well as LDL particle size. Rezulin also decreases LDL oxidation and Apo B levels. Taken collectively, these changes indicate that Rezulin may be increasing hepatic clearance of small, dense LDL (the more atherogenic subfractions of LDL) and producing larger, more buoyant, less atherogenic LDL.

Studies in the published literature indicate that, in addition to improving the lipid profile, Rezulin may also ameliorate atherosclerotic risk factors associated with vascular function. The effects of Rezulin on these parameters include:

- Increases in flow-mediated coronary dilation³⁴⁻³⁷
- Decreases in PAI-1 activity³⁸;
- Decreases in platelet activation³⁹; and
- Decreases in intimo-medial thickening⁴⁰⁻⁴³.

Troglitazone
Tablets

Table 5. Summary of Pivotal Parke-Davis Clinical Studies
(Page 1 of 2)

Study	Study Design	No. of Participants	Results of Primary Efficacy Analyses	
			Drugs, Dosage Regimen	Duration of Treatment
Combination With Insulin 991-040 ^{ref}	26-week double-blind, placebo- controlled, randomized, parallel-group study in patients with type 2 diabetes requiring insulin, with optional, open- label extension	118 PBO	PBO, or 200 mg TRG, or 600 mg TRG QAM; PBO switched to 400 mg TRG in extension, with no dose escalation	Baseline: 8 wk DB: 26 wk OL: 17 mo
		233 TRG		DB: Troglitazone-treated patients had a significantly greater (p < 0.01) responder rate ^a compared with patients who received placebo. Twenty-two percent of patients treated with 200 mg troglitazone and 27% of patients treated with 400 mg troglitazone were classified as responders compared with 7% of placebo-treated patients. Patients treated with 400 mg troglitazone reduced total daily insulin dose by 58%, and 15% discontinued insulin by the end of the double-blind phase. OL: Of the 173 patients who entered open-label, 87% were titrated to 400 mg/day. Insulin dose reductions were similar for this cohort in the double-blind and open-label phases, while HbA _{1c} decreased by 1% and FSG by 17-22% in open-label.
991-068 ^{ref}	26-week, double-blind, placebo- controlled, randomized, parallel-group study in patients with type 2 diabetes requiring insulin, with optional, open- label extension	71 PBO	PBO, or 200 mg TRG, or 400 mg TRG QAM; all began extension on 200 mg TRG	Baseline: 2-4 wk DB: 26 wk OL: 48 wk
		151 TRG		DB: Patients treated with 200 mg, 400 mg, and 600 mg troglitazone had significant (p ≤ 0.01) decreases in FSG compared with placebo at Week 26. Changes from baseline at Month 6 in HbA _{1c} were statistically different from placebo for troglitazone's 2 highest dose groups (p < 0.01). OL: Mean FSG continued to decline during the open-label phase.
Monotherapy 991-032 ^{ref}	26-week, double-blind, placebo- controlled, randomized, parallel-group study in patients with type 2 diabetes, with optional, open-label extension	80 PBO	PBO, or 100 mg TRG 200 mg TRG 400 mg TRG 600 mg TRG QAM; PBO switched to 200 mg TRG in OL	Baseline: 2 wk DB: 26 wk OL: 18 mo
		322 TRG		DB: Patients treated with 200 mg, 400 mg, and 600 mg troglitazone had significant (p ≤ 0.01) decreases in FSG compared with placebo at Week 26. Changes from baseline at Month 6 in HbA _{1c} were statistically different from placebo for troglitazone's 2 highest dose groups (p < 0.01). OL: Mean FSG continued to decline during the open-label phase.

^a Responders were patients with a ≥50% reduction from baseline in total daily insulin dose and either a ≥15% reduction in mean blood glucose or a mean blood glucose ≤140 mg/dL.
^b Mean blood glucose was defined as the average preprandial capillary blood glucose value for 7 days prior to a clinic visit.
 PBO = Placebo; TRG = Troglitazone; QAM = every morning; DB = Double-blind phase; OL = Open-label phase; FSG = Fasting serum glucose; HbA_{1c}: QD = Once daily; BID = twice daily.

Troglitazone
Tablets

Table 5. Summary of Pivotal Parke-Davis Clinical Studies
(Page 2 of 2)

Study	Study Design	No. of Participants	Results of Primary Efficacy Analyses	
			Drug Administration	Duration of Treatment
Combination With Sulfonylurea 991-055ref 991-093ref	12-month, double-blind, active-controlled, multicenter study in patients with type 2 diabetes who are sulfonylurea failures	473 TRG 79 GLY	Troglitazone 200, 400, and 600 mg, QD Micronized glyburide 12 mg BID	Baseline: 4-week glyburide DB: 52 wk OL: 72 wk
			Troglitazone 200 mg QD + 12 mg micronized glyburide BID Troglitazone 400 mg QD + 12 mg micronized glyburide BID Troglitazone 600 mg QD + 12 mg micronized glyburide BID DB dose maintained in OL with titration allowed	DB: There was a dose-related decrease in FSG at Week 52 for all combination therapy groups compared with glyburide (p < 0.0001). Decreases in FSG for the troglitazone monotherapies were not statistically different from glyburide. Patients treated with all doses of combination therapy had significant (p < 0.0001) decreases in HbA _{1c} compared with glyburide (-1.6% to -2.7%). A statistically significant increase in HbA _{1c} for the 200 mg troglitazone versus glyburide monotherapy comparison was found. Changes in HbA _{1c} for the 400 and 600 mg troglitazone monotherapies were not different from glyburide. OL: Of the 241 patients that entered open-label, 121 remained on double-blind therapy. The majority (69%) had been receiving troglitazone 400 mg/glyburide or troglitazone 600 mg/glyburide. Patients who received troglitazone 600 mg/glyburide during the double-blind phase had mean HbA _{1c} of 7.4% (improved from 9.5%); these patients maintained this level of 7.4% at Week 124. There were 120 patients who required titration to 400 or 600 mg combination therapy during open-label. The mean HbA _{1c} for patients in the 400 combination group was 7.9% at Week 124; for patients in the 600 mg combination group, the mean HbA _{1c} was 8.6% (improved from 9.5% and 10% at baseline, respectively).

* Responders were patients with a ≥50% reduction from baseline in total daily insulin dose and either a ≥15% reduction in mean blood glucose or a mean blood glucose ≤140 mg/dL. Mean blood glucose was defined as the average preprandial capillary blood glucose value for 7 days prior to a clinic visit.
PBO = Placebo; TRG = Troglitazone; QAM = every morning; DB = Double-blind phase; OL = Open-label phase; FSG = Fasting serum glucose; HbA_{1c}; QD = Once daily; BID = twice daily.

5. THE BENEFIT-RISK ASSESSMENT OF REZULIN THERAPY

A benefit-risk assessment of Rezulin must consider:

- First, the risks of uncontrolled diabetes are substantial, and treatment is required when diet and exercise fail to control blood glucose levels;
- Second, long-term studies have demonstrated secondary failures of other available therapies, so there is a clear medical need for therapies that help patients to achieve and sustain glycemic control;
- Third, Rezulin's unique mechanism of action, lack of renal effects, and lack of hypoglycemia make it especially relevant and useful in certain patient populations (e.g., early diabetes, elderly, patients with renal impairment);
- Fourth, the benefits of Rezulin are unique, complementary to other medications, and clinically proven to be sustained; and
- Fifth, the risks associated with Rezulin are rare, comparable to other therapies, and declining due to enhanced education practices and liver enzyme monitoring.

5.1. Risks Associated With Uncontrolled Diabetes

Diabetes mellitus is a serious health problem associated with high morbidity and mortality. It is a leading cause of death, and the leading cause of new cases of blindness and end-stage renal disease affecting approximately 16 million Americans.⁴⁴ Nearly 75% of patients with diabetes die of an atherosclerotic event, and the incidence of coronary artery and cerebrovascular disease is increased 2- to 4-fold in patients with diabetes.⁴⁵ Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). The Diabetes Control and Complications Trial (DCCT) found that intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM and reduces the risk of diabetes complications by 50% to 75%.⁴⁶

Troglitazone
Tablets

As a result of DCCT, the importance of glycemic control is widely accepted. The Kumamoto Study, a study in Japanese patients with type 2 diabetes, showed similar results to those observed in the DCCT in that intensive glycemic control with multiple insulin injections delayed the onset and the progression of diabetic retinopathy, nephropathy and neuropathy.⁴⁷

The United Kingdom Prospective Diabetes Study (UKPDS) provides added support that good glycemic control limits microvascular complications. UKPDS is a prospective, multicenter, randomized controlled trial, in patients with type 2 diabetes, with an objective to determine the most appropriate treatment modality to prevent or delay microvascular and/or macrovascular complications.^{48,49} The UKPDS provides clinically meaningful results in support of an intensive treatment policy, the benefits of which are a significant reduction in the development of microvascular complications (25% decrease) in patients with type 2 diabetes receiving insulin therapy as well as treatment with oral hypoglycemic agents. Epidemiological analysis of this data showed that for every percentage point decrease in HbA_{1c} there was a 35% reduction in the risk of complications.⁵⁰ In summary, several landmark studies have shown that improved glycemic control can reduce the long-term microvascular complications of diabetes and furthermore may have an impact on macrovascular complications.

Given that long-term glucose control is necessary to reduce the severe complications of diabetes, and the fact that approximately a substantial percentage of type 2 diabetes patients are unable to maintain glucose control, pharmacotherapy is a requirement for most patients.

5.2. Long-Term Failure of Other Therapies

Many type 2 diabetes patients are unable to maintain adequate glucose control, and treatment progresses from diet and exercise alone, to oral antidiabetic agents (individually and in combination), to insulin. It is important to note that there are only 4 classes of drug available for the treatment of type 2 diabetes in addition to Rezulin:

Troglitazone
Tablets

insulin, insulin secretagogues (sulfonylureas and repaglinide), metformin (biguanide), and alpha glucosidase inhibitors. Most of these therapies have been associated with secondary failures. For example, secondary failures with sulfonylureas beginning after 12 months as well as with insulin and metformin have been reported. Moreover, in the UKPDS trial, despite aggressive use of other available therapies (sulfonylureas, metformin, acarbose, and insulin), blood glucose levels rose in many patients over time.

These data demonstrate a clear gap in available therapies for type 2 diabetes. It is against the background of diabetes and its serious complications, and the therapeutic limitations of other available therapies, that one must evaluate the benefits and risks of Rezulin. As discussed below, Rezulin fills a significant therapeutic void, and clinical studies have confirmed its long-term benefits in the treatment of type 2 diabetes.

5.3. Clinical Trial Data: Efficacy and Sustained Effect of Rezulin

- Thirty percent of patients treated with insulin in combination with 200 mg Rezulin and 57% of patients treated with 600 mg Rezulin had an HbA_{1c} value below 8% at the end of the study, compared with 11% of placebo-treated patients (991-040).
- Improvement in HbA_{1c} for the sulfonylurea combination groups can also be seen in Study 991-055, where approximately 60% of patients at 600 mg Rezulin/12 mg glyburide had HbA_{1c} levels \leq 8% at Week 52 compared with baseline.
- A measure of the long-term effectiveness of Rezulin as monotherapy is demonstrated by the patients who began and remained on 600 mg Rezulin for the entire study. Of the 47 patients treated with 600 mg Rezulin during the double-blind and open-label phases, 21 patients had data at Month 24. Of these patients, 71% achieved an HbA_{1c} of \leq 8% and 62% of these patients achieved an HbA_{1c} of \leq 7%. (991 032 extension).
- Of the 241 patients that entered a sulfonylurea combination study, 121 patients remained on their double-blind therapy throughout the open-label phase. Sixty-one

Troglitazone
Tablets

percent of patients in the Rezulin 400 mg/glyburide group and 69% of patients in the Rezulin 600 mg/glyburide group had HbA_{1c} levels ≤8% at the end of the study. There were 120 patients who required titration to 400 or 600 mg combination therapy either at the onset or at some point during the open-label phase. Of these, 95 were qualified for data analysis (47 patients on 400 mg combination therapy and 48 on 600 mg combination therapy). Of these 95 patients who were not adequately controlled prior to titration, 53% were adequately controlled (HbA_{1c} of ≤8%) by the end of the study (991-093).

5.4. The Benefits of Rezulin Outweigh Associated Risks

As demonstrated above, Rezulin is associated with rare adverse liver events, the incidence of which is declining and comparable to risks of serious adverse events associated with other available therapies. Having demonstrated that Rezulin is not “less safe” than other therapies, we must evaluate whether the known risks are acceptable in light of the benefits provided by the drug. For the reasons discussed below, the answer to that question is affirmative. The benefits of Rezulin are significant, unique, and complementary to the disease process and other therapies:

- First, Rezulin reduces insulin resistance, a principal cause of the disease, through a unique nuclear mechanism of action that is not present in any drug on the market;
- Second, as initial therapy and in patients inadequately controlled with other diabetes medications, patients are able to achieve improved and sustained glycemic control with Rezulin treatment;
- Third, the improved, sustained glycemic control will translate into decreased risk for microvascular disease based on DCCT and UKPDS data; and
- Fourth, the non-glucose effects of Rezulin appear to confer additional benefits potentially altering atherogenic risk.

Based on the data, the benefits of Rezulin outweigh the risk of rare adverse liver events.

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Troglitazone
Tablets

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Troglitazone
Tablets

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Liver Enzyme Monitoring Recommendations in Rezulin® Labeling

July 1998 (Current)

Serum transaminase levels should be checked at the start of therapy, monthly for the first eight months of therapy, every two months for the remainder of the first year of Rezulin therapy, and periodically thereafter. Rezulin therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >1.5 times the upper limit of normal). Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. If serum transaminase levels are moderately increased (ALT >1.5 to 2 times the upper limit of normal), liver function tests should be repeated within a week and then weekly until the levels return to normal. If at any time a patient has jaundice or ALT rises above 3 times the upper limit of normal, Rezulin should be discontinued.

December 1997

It is recommended that serum transaminase levels be checked at the start of therapy, monthly for the first six months of therapy, every two months for the remainder of the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. Rezulin therapy should not be initiated if the patient exhibits clinical or laboratory evidence of active liver disease (eg, ALT >3 times the upper limit of normal) and should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT >3 times the upper limit of normal).

October 1997

It is recommended that serum transaminase levels be checked within the first one to two months and then every three months during the first year of troglitazone therapy, and periodically thereafter. Liver function tests also should be obtained for patients at the first symptoms suggestive of hepatic dysfunction, eg, nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. Rezulin should be discontinued if the patient has jaundice or laboratory measurements suggest liver injury (eg, ALT >3 times the upper limit of normal).

Patient prescription activity is captured from the Source Retail Pharmacy database, composed of prescriptions dispensed in more than 35,000 US retail pharmacies. All forms of payment (Cash, Medicaid, and Third Party) are included. A subset of the national sample of more than 11,000 of these stores provide a patient identifier and can be used in patient studies such as New Therapy Starts and Persistency data.

1. NEW THERAPY STARTS

To determine the number of new patients each month, all patients filling a prescription for Rezulin and all other antidiabetic products in the month are selected from the database. Patients are categorized as “new” if they filled no script for the specified product during the prior six months. Patients classified as new to the product may have had prior antidiabetic therapy. The new patient counts are then projected using Source Prescription Audit (projected national total prescriptions, similar to IMS TRx’s).

2. PERSISTENCY

Patients are categorized as “new” if they filled no script for Rezulin during the prior six months. All patients that meet that qualification are tracked as a cohort going forward to determine if they are still on Rezulin therapy. A 35-day grace period is used to allow for non-compliance. Patient are persistent in a given month if they fill the Rx in the month being evaluated or their day’s supply plus a 35-day grace period shows them as on therapy in that month. Patients are considered off therapy if they don’t meet either of the previous requirements.

APPENDIX 4

United States Death and Transplant Cases

1. File MCN# 001-0991-970813 [Transplant]

Forty-nine year old female with type 2 diabetes on insulin, hypertension and hyperlipidemia. Past medical history: hepatitis A and cholecystectomy. Concomitant medications: lisinopril, gemfibrozil, estradiol, Provera, potassium, Tempro (contains acetaminophen). Normal liver function documented prior to initiation of troglitazone, 200 mg/day on 15MAR97. Dose increased to 400 mg/day on 11JUL97. Three weeks later the patient developed malaise, nausea and vomiting. Liver transaminases and bilirubin elevated. Troglitazone and gemfibrozil discontinued. Hepatitis serology positive for Hepatitis A antibody, otherwise negative. Imaging of liver negative for obstruction. Progressive liver failure requiring liver transplant on 26SEP97. Considered to be recovered as of 13NOV97.

LFTs: May 1996: ALT=22 and/or 23; AST=18 and/or 22
Oct 1996: within normal limits
Aug 1997: ALT=1316; AST=684; direct/total bili=2.9/4.8
Sep 1997: bili=15-29; ALT=1800; AST=1800

2. File MCN# 001-0991-970987

Forty-six year old male type 2 diabetic on insulin. Obese, non-compliant, poorly controlled. Past medical history: mild elevation of serum bilirubin in AUG96. Concomitant medications: none. Troglitazone 200mg/day begun 31MAR97. Dose increased gradually to 600 mg/day by JUL97. Presented 01AUG97 with malaise, nausea, vomiting. Treated with chlorperazine. Hospitalized 13AUG97 with jaundice, elevated liver transaminases. Negative viral serology. Progression to hepatic coma, considered for liver transplantation but patient died 22AUG97. Autopsy report: "Non A, B, C fulminant viral hepatitis".

LFTs: 08/13/96: total bili=1.5
08/13/97: ALT=2000; AST=1836; total bili=15.9

3. File MCN# 001-0991-973037

Eighty-five year old, poorly controlled, type 2 diabetic male on insulin. Past medical history: hypertension, hypothyroidism. Concomitant medications: thyroxine, metoprolol. Troglitazone 200mg/day begun JUN97 and increased to 400mg/day after 15 weeks. Presented 4 weeks later with malaise, abdominal pain, jaundice. Negative viral serology. Normal liver ultrasound. Liver biopsy: massive hepatic necrosis. Death in JAN98 from progressive liver failure.

LFTs: 10/30/97: ALT=300; AST=300; total bili>2.0
11/25/97: ALT=287; AST=416; total bili=15.6
11/26/97: ALT=300; AST=300; total bili=12.0
12/29/97: ALT=300 and 608; AST=200; total bili=16.0

4. File MCN# 001-0991-973131 [Transplant]

Fifty-nine year old, obese female with type 2 diabetes complicated by retinopathy, nephropathy and neuropathy, on insulin. Past medical history: cholecystectomy, hysterectomy, renal calculi, recurrent hematuria, pyuria, medullary sponge kidney (creatinine 1.5 "baseline"), and mild elevation of AST (40, with ULN 37) and alkaline phosphatase (152, with ULN 136) with normal ALT noted one year before troglitazone begun. Concomitant medications: sulfamethoxazole/trimethoprim, cisapride. Troglitazone started at 400 mg/day on 12AUG97 and discontinued 3DEC97. Patient developed nausea and vomiting two weeks after starting troglitazone, and dark urine noted at 2 months, but did not report these symptoms. Patient self-discontinued troglitazone at 3.5 months; developed jaundice at 4 months. Hospitalized and developed progressive encephalopathy, protime increased, and underwent liver transplant 3 weeks after stopping troglitazone therapy. No other causes had been identified for liver failure (negative viral serology, imaging). Liver biopsy: severe parenchymal extinction and replacement by scar tissue. Liver transplant performed in DEC97 with good function during subsequent 4 months of observation.

[Brent A. Neuschwander-Tetri, M.D., et al. Troglitazone-Induced Hepatic Failure Leading to Liver Transplantation. *Annals of Internal Medicine*, 1 July 1998. 129:38-41]

LFTs: 12/--/96: ALT=55; AST=40
12/10/97: ALT=405; AST=797; direct/total bili=6.8/8.7
12/11/97: ALT=431; AST=856; direct/total bili=8.0/9.8
12/14/97: total bili=16.0
12/17/97: ALT=157; AST=262; total bili=16.3

5. File MCN# 001-0991-973146

Forty-five year old male, morbidly obese, type 2 diabetic on insulin. Past medical history: schizophrenia, asthma, hypertension, cocaine abuse, positive hepatitis B serology, Crohn's disease. Concomitant medications: paroxetine, lithium, Lodine, trifluoperazine, hydrochlorothiazide. Troglitazone 400mg/day begun MAR97. Baseline liver function tests minimally elevated (unspecified values). Troglitazone stopped on unknown date prior to admission in SEP97 with evidence of sepsis. Patient hospitalized 09SEP97. Abnormal liver function tests noted. Cocaine detected in blood. CT scan revealed chronic hepatic cirrhosis, splenomegaly, portal hypertension, and ascites. Died 24SEP97 from streptococcus septicemia and hepatic coma. No autopsy performed.

LFTs: baseline LFTs minimally elevated

6. File MCN# 001-0991-973212

Forty-six year old female type 2 diabetic on insulin. Past medical history: chronic anemia, morbid obesity, pulmonary hypertension, long history of cirrhosis with chronically elevated liver enzymes. Concomitant medications: multiple other medications. Troglitazone 400 mg/day begun 01JUN97; discontinued 1NOV97. Admitted to hospital 01NOV97 in liver failure. Death on 11NOV97. Autopsy report: cirrhosis.

LFTs: unknown

7. File MCN# 001-0991-980105

Sixty-five year old male type 2 diabetic on insulin. Past medical history: chronic hepatitis B (elevated ALT). Concomitant medications: unknown. Troglitazone begun on 04JUN97 at 200mg/day with dose increased to 400 mg/day two weeks later. No subsequent follow-up. Presented on 20NOV97 with jaundice, elevated transaminases. Hospitalized 13DEC97 with acute liver failure. Death from sepsis/hepatorenal syndrome on 14DEC97.

LFTs: 05/21/97: ALT=67; AST=42; total bili=1.0
06/04/97: ALT=67; AST=42; total bili=1.0
11/20/97: AST=296; total bili=5.9
12/13/97: AST=229; total bili=7.8

8. File MCN# 001-0991-980164

Sixty-two year old female type 2 diabetic on insulin and metformin. Past medical history: mitral valve replacement, two cerebro-vascular accidents, CHF. Concomitant medications: simvastatin, cisapride, digoxin, bumetamide, diltiazem, warfarin, ranitidine, paroxetine, estrogen/progestogen. Troglitazone 600mg/day begun on an unknown date in 1997. Hospitalized on 01DEC97 with pulmonary edema. Noted to have elevated liver transaminases and lactic acidosis. Troglitazone and metformin discontinued but troglitazone recommenced at 400mg/day on 15DEC97 and discontinued on 22JAN98 following rehospitalization on 22JAN98 with pneumonia, liver, renal and respiratory failure, severe acidosis. Following a cardiac arrest 23JAN98 she was ventilated and dialyzed, but died on 27JAN98.

LFTs: 12/--/97: ALT=736; AST=1423; total bili=0.57 and 0.7 and 0.95 and 2.62
01/12/98: ALT=10; AST=16
01/22/98: AST=1029
01/25/98: ALT=3600 and 736 and 4288 and 2478; AST=4200 and 1423 and 9518 and 1535

9. File MCN# 001-0991-980219

Seventy-seven year old female type 2 diabetic on glibenclamide. Past medical history: hypertension, renal disease, vascular disease (lower limbs, carotids). Concomitant

medications: pravastatin, amlodipine. Troglitazone 200 mg begun SEP97, discontinued 10DEC97. Presented 10DEC97 with jaundice. Normal liver function previously (AUG97). During admission, gastrointestinal bleeding from gastric ulcer precipitated hepatic coma in the setting of elevated liver transaminases. Gallstones detected but no obstruction noted on ERCP. Death from hepato-renal syndrome on 24JAN98.

LFTs: Aug 1997: LFTs normal
Sep 1997: LFTs normal
Dec 1997: LFTs 20 x normal; bili=4.5
12/12/97: LFTs "in the thousands"; bili=5.4

10. File MCN# 001-0991-980316

Seventy year old male type 2 diabetic began troglitazone (date not specified) in 1997. Past medical history: unknown. Concomitant medications: unknown. Drug discontinued in DEC97, following onset of jaundice. Hospitalized in mid-JAN98. Liver biopsy: extensive necrosis. Despite improvement (but not normalization (bilirubin approximately 3.0) of liver function, death from sepsis in late APR98.

LFTs: 01/15/98: ALT "in the thousands"; AST "in the thousands";
total bili=25.0 and 19 on readmission with plateau at 10-12

11. File MCN# 001-0991-980608

Fifty-five year old female type 2 diabetic on insulin. Past medical history: alcoholism, hypertension, hypothyroidism, back problems. Concomitant medications: levothyroxine, trazodone. Troglitazone (dose not specified) begun JAN98 and discontinued MAR98. Presented in MAR98 with jaundice. Liver biopsy: chronic hepatitis, possible auto-immune hepatitis versus fulminant drug-induced hepatitis with bridging portal fibrosis and cirrhosis, massive hepatocellular necrosis. Patient became unconscious, required intubation, developed pneumonia and died 05APR98.

LFTs: 02/--/98: ALT in 300s
03/--/98: total bili=30.0
03/27/98: ALT=248; AST=301; total bili=26.0

12. File MCN# 001-0991-980615

Sixty-four year old obese female type 2 diabetic on glipizide. Past medical history: hyperlipidemia, diabetic retinopathy, laser surgery on the right eye, hypertension, medical noncompliance, obesity, and a total abdominal hysterectomy secondary to fibroid. Concomitant medications: pravastatin, amlodipine, benazepril, verapamil, lisinopril, hydrochlorothiazide. Troglitazone 400mg/day begun 28NOV97. Normal liver function tests in NOV97, JAN98. Presented with jaundice, elevated transaminases on 20MAR98 and hospitalized on 02APR98. Troglitazone discontinued on 20MAR98 and pravastatin on 10MAR98. Progressive deterioration following admission. Abdominal ultrasound: cirrhosis, ascites. Liver transplant not considered (patient a Jehovah's witness

and refused blood products). Death on 14APR98 from "multisystem" organ failure.

LFTs: 11/28/97: ALT=14; AST=12; total bili=0.6
01/20/98: ALT=47; AST=30; direct bili=0.1; indirect bili=0.4; total bili=0.5
03/20/98: ALT=3000; AST=2940; direct bili=5.6; indirect bili=5.6; total
bili=11.2
03/24/98: ALT=3033; AST=3486; direct bili=12.6; indirect bili=5.5; total
bili=18.1
03/31/98: ALT=2940; AST=3340; direct bili=15.0; indirect bili=15.0; total
bili=30.0
04/02/98: ALT=2724; AST=2693; total bili=19.6
04/09/98: ALT=1277; AST=972; total bili=20.9 and 20.5

13. File MCN# 001-0991-980650 [Transplant]

Sixty-one year old female type 2 diabetic on insulin. Past medical history: Hypothyroid. Concomitant medications: thyroxine, estrogen/progestogen hormone replacement therapy. Troglitazone (dose not specified) used between DEC97 and MAR98. Presented with symptoms of liver failure in MAR98. Negative viral serology. Liver biopsy: extensive necrosis. Progressive deterioration (liver transplant in APR98. Post transplant course notable for mild rejection and biliary stricture, which required surgical revision. Patient doing well in JUL98.

LFTs: 12/03/97: AST=11; total bili=0.5
03/--/98: ALT=1400; AST=1200-1300
03/--/98: ALT and AST "in the 200s"
03/04/98: AST=252; total bili=0.5
04/14/98: total bili=9.4 and 12.7
04/15/98: ALT=300-500 and 264; AST=300-500 and 290

14. File MCN# 001-0991-980701

Eighty-one year old female type 2 diabetic. Past medical history: hypertension. Concomitant medications: unspecified anti-hypertensive. Troglitazone 400mg/day begun 15DEC97. Mildly abnormal liver function tests noted on 15JAN98 with further increase on 15FEB98; advice to cease troglitazone not followed until after 24APR98 when patient presented with jaundice. Antinuclear antibody positive at 1:640. Death from hepatic failure on 8MAY98.

LFTs: 10/10/96: AST=214; total bili=0.9
02/26/98: ALT=29; AST=63; direct/total bili=0.5/1.4
04/24/98: ALT=141; AST=334; direct/total bili=3.4/7.2
04/30/98: AST=218; direct/total bili=8.5/8.4
05/01/98: AST=221; total bili=21.3
05/05/98: ALT=90; AST=191

15. File MCN# 001-0991-980723

Sixty-five year old female type 2 diabetic on insulin. Past medical history: hypertension, diabetic nephropathy, retinopathy, neuropathy, infected foot ulcers, osteomyelitis, diverticulitis, chronic anemia, peripheral edema, hypercholesterolemia, cardiac dysrhythmia. Concomitant medications: enalapril, augmentin, calcium, Tylenol, Bactroban. Troglitazone 400mg/day begun 10JAN98. During initial six weeks on troglitazone, patient nauseated, fatigued, unable to eat. Troglitazone discontinued on 24MAR98 because of anorexia, jaundice, abnormal liver function. Hospitalized in APR98 with liver failure, coagulopathy, infected foot ulcer, and osteomyelitis requiring amputation to control infection. No other causes of liver disease identified. Progressive deterioration, hepatic encephalopathy, hepatic failure, and death on 09MAY98.

LFTs: 09/28/95: AST=17; total bili=0.4
10/04/96: AST=13
02/--/98: ALT<3xULN; AST=<3xULN
02/18/98: ALT=139; AST=107; direct/total bili=0.4/0.7
03/--/98: ALT about 1200; AST about 1200
03/16/98: ALT=798; AST=647; total bili=1.6
03/27/98: ALT=693; AST=844; direct/total bili=3.5/4.4
04/03/98: ALT=732; AST=1175; direct/total bili=9.5/10.9
04/06/98: ALT=672; AST=973; direct/total bili=11.9/13.6
04/13/98: ALT=517; AST=815; direct/total bili=16.5/18.4
04/15/98: ALT=482; AST=795; direct/total bili=16.5/18.6
04/17/98: ALT=466; AST=649; direct/total bili=17.1/19.2
04/21/98: ALT=375; AST=497; direct/total bili=12.9/19.0
04/25/98: ALT=272; AST=362; direct/total bili=11.6/17.6
04/26/98: ALT=221; AST=239; total bili=17.1
04/27/98: ALT=214; AST=181; direct/total bili=8.3/15.2
04/28/98: AST=177 and 213; total bili=14.6
04/29/98: AST=181; total bili=14.6
04/30/98: ALT=211; AST=134; direct/total bili=7.0/13.0
05/01/98: ALT=158; AST=134; direct/total bili=8.4/14.4
05/02/98: ALT=144; AST=132; direct/total bili=10.3/16.3 and 15.4
05/03/98: ALT=130; AST=119
05/05/98: ALT=87
05/05/98: AST=90
05/06/98: total bili=19.6

16. File MCN# 001-0991-980754

Seventy-seven year old female type 2 diabetic on glibenclamide and metformin. Past medical history: cardiac arrhythmias and allergies to codeine and cortisone. Concomitant medications: digoxin and Dyazide. Troglitazone 200mg/day begun DEC97; stopped 22APR98. Normal (normal ALT = 5-30 units) liver function pre-treatment but mild elevation of transaminases noted 31MAR98. Hospitalized 22APR98 with jaundice, and

troglitazone discontinued. Gallstones demonstrated but no obstruction or other pathology on ERCP/CT scan. Initial improvement in liver function followed by deterioration and death from liver failure on 19JUN98.

LFTs: 12/27/97: ALT=14.0
02/07/98: ALT=15.0
03/21/98: ALT=69
03/31/98: AST=mild elevation
04/22/98: ALT=590; AST=848; direct/total bili=13.2/20.6
05/10/98: ALT=186; AST=266; direct/total bili=9.3/15.7
05/30/98: total bili=25.2
05/31/98: ALT=373; AST=845; direct/total bili=14.4/23.1
06/04/98: AST=750; total bili=25.3
06/18/98: ALT=129; AST=321; total bili=15.7

17. File MCN# 001-0991-980772

Fifty-seven year old female type 2 diabetic. Past medical history: obesity, hypertension, fatty liver, "liver disease for many years" (per reporting physician), hyperlipidemia, Hashimoto's thyroiditis. No concomitant medications specified. Troglitazone 400mg/day begun SEP97; discontinued APR98. No monitoring of liver function due to patient's failure to follow up. Presented in MAY98 with hepatic failure and encephalopathy. Death on 12MAY98. Autopsy report: "long-standing micronodular cirrhosis of unknown etiology".

LFTs: 12/06/97: ALT=64; AST=68; total bili=0.4
12/17/98: ALT=46; AST=58; total bili=0.3

18. File MCN# 001-0991-980812

Fifty-five year old female participating in NIH-sponsored clinical trial of troglitazone in the prevention of progression of impaired glucose tolerance to diabetes (Protocol # 991-098). Past medical history: none reported. Concomitant medications: none. Troglitazone (dose not specified) begun 12JAN98. Patient experienced "flu-like" syndrome between 12FEB98 to 15FEB98 and from 07MAR98 to 08MAR98. Previously normal transaminases noted to be elevated on 10MAR98. Troglitazone discontinued on 17APR98, four days after further elevation in transaminases noted. Admission to hospital on 02MAY98 with jaundice, nausea, vomiting, abdominal pain. Liver biopsy: lobular hepatitis, viral or drug etiology. CMV infection suggested by positive serology and immunostaining. Progressive deterioration. Liver transplant performed 16MAY98 but extensive large bowel necrosis necessitating colectomy resulted in death on 17MAY98. No autopsy.

LFTs: 10/16/97: ALT=15; AST=22
02/12/98: ALT=16; AST=14
03/10/98: ALT=89; AST=55

04/13/98: ALT=933; AST=586
 04/20/98: ALT=1090; AST=667
 04/23/98: total bili=1.6
 05/02/98: ALT=1382; AST=1290
 05/03/98: ALT=714; AST=543
 05/04/98: ALT=1158; AST=597
 05/14/98: ALT=1496; AST=106

19. File MCN# 001-0991-980859 [Transplant followed by Death]

Forty-nine year old female diabetic (type unclear) on insulin and glibeclamide. Past medical history: stomach problems. Concomitant medications: ranitidine, metoclopramide. Troglitazone 200mg/day begun 27OCT97. Normal baseline liver function tests on 05NOV97 but markedly elevated transaminases noted on 10APR98 when troglitazone use discontinued. Hospitalized on 14APR98 and several times thereafter, with progressive deterioration in liver function (total bilirubin of 17, alkaline phosphatase 191, AST 866, ALT 824) and glycemic control, development of coagulopathy (preventing liver biopsy), orthostatic hypotension, hepatic encephalopathy, possible sepsis, acute myocardial infarction, acute renal failure and death on 21MAY98.

LFTs: 11/05/97: ALT=11; AST=18
 04/10/98: ALT=1088; AST=1248
 04/15/98: ALT=1789; AST=1814; direct bili=2.8
 04/17/98: ALT=1789; AST=1814
 04/19/98: total bili=4.6
 04/28/98: ALT=1592; AST=1645; direct/total bili=1.8/5.2
 05/05/98: ALT=1316; AST=1377; direct/total bili=3.24/8.7
 05/15/98: total bili=4.4
 05/18/98: ALT=824; AST=866; direct/total bili=8.9/17.5 and 20.0

20. File MCN# 001-0991-980900

Seventy-two year old female type 1 diabetic on insulin and glipizide. Past medical history: Hashimoto's thyroiditis, hypertension. Concomitant medications: thyroxine, digoxin, enalapril, spironolactone. Troglitazone 200mg/day begun 02MAY97 and used intermittently until 16SEP97. Intermittent use of the drug was due to patient's perception that it was causing symptoms of heartburn and loose stools. Hospitalized 23SEP97 with evidence of fluid retention, liver dysfunction. Ultrasound showed liver cirrhosis. Positive hepatitis B serology. Following an initial improvement and discharge from hospital she was re-admitted with hypotension, congestive cardiac failure, urinary sepsis and septicemia. Death on 06OCT98 from hepatorenal failure with encephalopathy. No autopsy.

LFTs: 04/15/97: total bili=0.4
 09/22/97: direct bili=2.8; total bili=4.6;
 09/24/97: AST=804 and 867; direct bili=3.1; total bili=5.6 and 5.3

09/25/97: AST=790; direct bili=2.7; total bili=5.3
09/26/97: AST=901; direct bili=2.7 and 3.3; total bili=5.2 and 6.1
09/27/97: AST=641; direct bili=3.4; total bili=6.3
09/28/97: AST=526; direct bili=3.5; total bili=6.7
09/29/97: AST=379; direct bili=3.2; total bili=6.4
09/30/97: AST=402; direct bili=3.4; total bili=6.8
10/01/97: AST=371; direct bili=3.6; total bili=6.5
10/03/97: AST=289

21. File MCN# 001-0991-980949

Eighty-four year old male type 2 diabetic on glibenclamide. Past medical history: ischemic heart disease with MI and angina, recurrent congestive failure, cholecystectomy, prostatectomy, hypothyroidism. Concomitant medications: thyroxine, furosemide, captopril, metolazone, isosorbide. Troglitazone 400mg/day began NOV97. Hospitalized 29DEC97 with cerebrovascular accident. Developed jaundice, elevated liver transaminases and acute renal failure. Troglitazone discontinued 02JAN98 but liver dysfunction persisted and patient died 07JAN98 from hepatorenal failure and CVA with left hemiparesis.

LFTs: 01/01/98: ALT=541; AST=199; total bili=5.4
01/05/98: ALT=290; AST=68; total bili=7.9

22. File MCN# 001-0991-981478

Fifty-two year old female with type 1 diabetes, on insulin. Past medical history: hypothyroidism, hypercholesterolemia, penicillin and shellfish allergy. Concomitant medications: levothyroxine, simvastatin, lansoprazole. Troglitazone 400mg/day begun DEC97 for insulin resistance; discontinued JUN98. Presentation in FEB98 with fatigue and jaundice (bilirubin level 28.9 mg/dL; alanine aminotransferase (ALT) level 1227 U/L; alkaline phosphatase level 216 U/L; prothrombin time 15.2 seconds; albumin level 2.4 g/dL). Neither troglitazone nor simvastatin discontinued until JUN98. Liver biopsy: extensive hepatocellular necrosis. Patient's hospital course characterized by progressive cholestasis, with a peak bilirubin of 46.8 mg/dL and alkaline phosphatase of 324 U/L. While being evaluated for liver transplant, patient became septic and died on 24JUL98. No autopsy was performed.

[Steven K Herrine, M.D., et al. Severe Hepatotoxicity Associated with Troglitazone. Annals of Internal Medicine ; 19 January, 1999]

LFTs: 06/--/98: ALT=1227; total bili=28.9
06/25/98: ALT=564; AST=362; direct/total bili=22.8/37.8 and 20.0

23. File MCN# 001-0991-981674 [Transplant followed by Death]

Fifty-three year old female, type 2 diabetic on glipizide and metformin. Past medical history: chronic hepatitis B, liver disease with fibrosis, hypertension, stroke with LUE weakness. Concomitant medications: amlidopine, Ticlid, Lotensin. Troglitazone 400mg/day begun 11FEB9; discontinued on unknown date. Normal liver function reported subsequently. Onset of "flu-like" illness while on European trip. Hospitalized in AUG98 with jaundice and evidence of liver failure. Multiple investigations including viral serology and liver biopsy - conflicting results suggestive of viral hepatitis but a conclusion that the liver failure was secondary to troglitazone was reached. Patient underwent a liver transplant 10SEP98 but died 21SEP98.

LFTs: 07/20/95: ALT=30; AST=27; total bili=1.0
12/18/97: ALT=19; AST=19; total bili=0.6
02/05/98: ALT=20; AST=19; total bili=0.5
04/06/98: ALT=15; AST=16; total bili=0.5
06/08/98: ALT=21; AST=19
??/??/?? ALT=531; AST=534; total bili=21.4

24. File MCN# 001-0991-981695

Eighty year old male type 2 diabetic on insulin and glipizide. Past medical history: questionable history of hepatitis A, cholecystectomy, appendectomy, alcohol consumption, possible stomach ulcer. Concomitant medications: aspirin, vitamin K. Troglitazone 200mg/day begun 09APR98; discontinued 15JUL98. Normal liver function tests in MAY98, markedly abnormal on 13JUL98 (albumin 3.6, total bilirubin 7.6, direct bilirubin 5, alkaline phosphatase 112, serum AST 682, serum ALT 1270) when patient admitted with jaundice and liver failure. He developed hepatic encephalopathy, hepatorenal syndrome and coagulopathy, and died 02SEP98.

LFTs: 05/18/98: ALT=32; AST=26; total bili=1.2
07/13/98: ALT=1270; AST=682; direct/total bili=5.0/7.6
07/17/98: ALT=1574; AST=978; direct/total bili=6.7/10.3
07/30/98: ALT=1344; AST=1061; direct/total bili=14.8/27.9
08/04/98: ALT=772; AST=628; direct/total bili=15.2/30.8
08/06/98: ALT=561; AST=434; direct/total bili=15.3/24.1
08/12/98: ALT=345; AST=276; total bili=25.0
08/13/98: ALT=327; AST=250; direct/total bili=16.0/27.4
08/14/98: ALT=299; AST=217; direct/total bili=11.4/27.3
08/15/98: ALT=283; AST=214; direct/total bili=14.4/28.3
08/17/98: ALT=250; AST=186; total bili=25.8
08/18/98: total bili=27.6
08/19/98: ALT=281; AST=228; total bili=27.7
08/20/98: ALT=289 and 332; AST=233 and 264; direct/total bili=16.3/26.3
08/26/98: total bili=31.5
08/28/98: direct/total bili=24.0/32.0

25. File MCN# 001-0991-981763

Seventy year old female type 2 diabetic on glipizide and repaglinide. Past medical history: heart problems, congestive heart failure, chronic renal impairment, hyperlipidemia, CABG, atrial fibrillation. Concomitant medications: lovastatin, aspirin, Bumex, Zaroxolyn, Prempro. Troglitazone 400mg/day begun 22MAY98 and dose increased to 600mg/day on 03SEP98. Normal liver function on 03SEP98. Crushing injury to legs suffered on 09SEP98. Hospitalized on 13SEP98 with severe weakness, markedly abnormal liver function, hemoglobin = 7.5, disseminated intravascular coagulation. Cardiac arrest death on 14SEP98 with severe metabolic acidosis. No autopsy was performed.

LFTs: 02/01/98: AST=23; total bili=0.7
03/12/98: ALT=18; AST=16; total bili=0.5
04/15/98: ALT=17; AST=17; total bili=0.5
05/11/98: ALT=17; AST=19; total bili=0.7
06/22/98: ALT=23; AST=18; total bili=0.8
07/23/98: ALT=23; AST=19; total bili=0.5
09/03/98: ALT=24; AST=22; total bili=0.5
09/13/98: total bili=1.5
09/14/98: ALT=4082; AST=3477; total bili=2.1

26. File MCN# 001-0991-981964 [Transplant]

Sixty-one year old female with diabetes. Past medical history: hypercholesterolemia. Concomitant medications: unknown. Started troglitazone 400mg daily and atorvastatin 10mg daily in NOV97. No baseline liver function tests were provided. In APR98, laboratory tests revealed that the liver function tests were increased (no specific values were provided). Both therapies ended in MAY98. Diagnosis of liver failure; on 2OCT98, the patient underwent a liver transplant.

LFTs: 04/--/98: LFTs increased
06/--/98: LFTs abnormal

27. File MCN# 001-0991-981992

Eighty-one year old female, type 2 diabetic. Past medical history: unknown. Concomitant medications: unknown. Troglitazone begun 01APR98; stopped 01AUG98. Hysterectomy JUN98, developed hepatic failure AUG98. Expired 24SEP98 due to encephalitis secondary to hepatitis with DIC, renal failure, and hepatic failure.

LFTs: 08/--/98: LFTs increased
09/--/98: total bili>14

28. File MCN# 001-0991-982272

Sixty-three year old female. Past medical history: alcoholism strongly suspected.

Troglitazone begun 09OCT98; ended 19NOV98. Developed hepatorenal syndrome, hepatic encephalopathy with asterixis noted 09DEC98. Death 18DEC98. Final diagnosis "fulminant hepatic failure."

LFTs: 10/09/98: ALT=17; AST=24; total bili=1.16
11/06/98: ALT=22; AST=38
11/19/98: ALT=1130; AST=1170; direct/total bili=1.9/4.3
11/23/98 ALT=1083 and 1270; AST=1406 and 1194; direct/total bili=3.6/9.2
11/24/98: AST=1149
12/03/98: ALT=491; AST=247; total bili=26.5
12/14/98: ALT=86; AST=95; total bili=31.4
12/17/98: AST=54; total bili=37.7

29. File MCN# 001-0991-982275

Sixty-five year old male. Past medical history: sick sinus syndrome, pacemaker placed in 1992, elevated PSA, mildly elevated LFT's in 1995. Concomitant medications: Accupril (quinapril), Coumadin (warfarin), Cardene (nicardipine) and Cardura (doxazosin). Patient began amiodarone on an unknown date for heart disease. Troglitazone begun approximately JUL98. Patient developed liver failure on an unknown date in 1998. Troglitazone and amiodarone discontinued on an unknown date. Expired 08NOV98.

LFTs: unknown

30. File MCN# 001-0991-982300

Ninety-one year old female. Past medical history: Alzheimer's dementia. Concomitant medications: Aricept (donepezil). Troglitazone begun 26OCT98; ended 13NOV98. The patient was apparently well until 11NOV98 when she was presented to the ER because she complained of dizziness and weakness that day; she was found to be short of breath and diaphoretic. She was febrile in the ER, 101F. Her blood pressure was 90 - 100/60 - 70, was as low as 68/53 and dopamine given. She was noted to have atrial fibrillation. Her chest X-Ray (CXR) revealed small right lung infiltrate, cardiac enlargement and no acute failure. On 07OCT98, the patient's AST 23 U/L (15 - 40), alkaline phosphatase 84 U/L (37 - 91) and total bilirubin .7 mg/dL (.3 - 1.3). Hospitalized; diagnosed with fulminant hepatocellular toxicity, renal failure and new onset atrial fibrillation. AST 2160 U/L, ALT 2880 U/L (4 - 44), total bilirubin 2.4 mg/dL, LDH 1698 U/L (81 - 170), BUN 73 mg/dL, creatinine 3.6 mg/dL. Hepatitis B titer was positive. On 11NOV98, ultrasound of the abdomen revealed dilated common bile duct and gall stones, with a possible intraductal stone. After admission, the patient's condition rapidly deteriorated. She became acidotic and expired 15NOV98. No autopsy was done.

LFTs: 10/07/98: AST=23; total bili=0.7
11/11/98: AST=600; direct/total bili=1.1/2.2
11/12/98: AST=10,700; direct/total bili=1.2/2.2

11/13/98: ALT=2880; AST=2160; direct/total bili=1.6/2.4
11/14/98: ALT=2210; AST=1000; direct/total bili=1.4/2.3

31. File MCN# 001-0991-982370 [Transplant]

Forty-nine year old female with type 2 diabetes, on glipizide. Past medical history: hypothyroid, peptic ulcer disease, upper GI bleed, hypertension. Concomitant medications: levothyroxine and quinapril. Troglitazone 400mg started 10JUN98; ended 03NOV98. Presented with jaundice, developed liver necrosis and abdominal swelling. On 01AUG98, LFT's were normal. On 30OCT98, the patient's lab values were: AST 1150 (1 - 40), ALT 1422 (1 - 50) and total bilirubin 12.4 (0.2 - 1.4). The patient's lab values on 30DEC98 were: AST 120, ALT 194, alkaline phosphatase 249 and total bilirubin 32.8. Patient underwent a liver transplant 7JAN99, postoperatively became septic with fungemia.

LFTs: 08/01/98: ALT=13; AST=14; total bili=0.4
10/30/98: ALT=1422; AST=1150; total bili=12.4
11/03/98: ALT=1067; AST=840; total bili=15.5
11/11/98: ALT=447; AST=399; total bili=19.1
11/13/98: ALT=326; AST=261; total bili=26.7
11/25/98: ALT=83; AST=120; total bili=24.6
12/09/98: ALT=106; AST=157; total bili=30.8
12/30/98: ALT=194; AST=120; total bili=32.8

32. File MCN# 001-0991-990090

Seventy year old male with type 2 diabetes on insulin. Past medical history: obesity, congestive heart failure, CABG, hypertension, coronary artery disease, atrial fibrillation, carotid artery disease, chronic renal insufficiency, prior use of carbon tetrachloride. Concomitant medications: Lopressor, digoxin, Lasix, Zaroxolyn, Paxil, Imdur, K-dur. Troglitazone started about OCT98; stopped 21DEC98. Patient developed hepatomegaly, splenomegaly, hepatic necrosis, sludge in gallbladder, leukocytosis, ascites. In DEC98, noted to be jaundiced. On 21DEC98 admitted for work-up: AST 71, ALT 54, bilirubin 10, alkaline phosphatase 343, sonogram showed abnormal gallbladder; discharged 24DEC98. On 31DEC98 went to ER with fever, chills, deepening jaundice and suspicion of obstructive jaundice. On 01JAN99 under went ERCP with sphincterotomy and had Group B streptococcus septicemia. He was admitted; rapidly deteriorated, and died 09JAN99. Autopsy revealed hepatomegaly with massive hepatic necrosis, splenomegaly, and ascites.

LFTs: 03/--/98: AST=17
07/--/98: AST=36; total bili=1.03
12/21/98: ALT=54; AST=71; direct/total bili=9.0/10.0
12/24/98: ALT and AST slightly decreased; direct and total bili elevated
12/28/98: ALT and AST mildly elevated; direct/total bili=19/24
12/31/98: ALT and AST mildly elevated; total bili=26

01/02/99: ALT=76; AST=118; direct/total bili=22.5/26.0
 01/03/99: ALT=153; AST=278; direct/total bili=24.2/26.7
 01/04/99: ALT=318; AST=648; direct/total bili=25.5/29.2
 01/05/99: ALT=358; AST=748; direct/total bili=23.9/25.8
 01/06/99: ALT=496; AST=1028; direct/total bili=25.6/27.0
 01/07/99: ALT=473; AST=1022; direct/total bili=23.1/24.5
 01/08/99: ALT=518; AST=1119; direct/total bili=22.3/23.7

33. File MCN# 001-0991-990153 [Transplant]

Unknown age female. Past medical history: unknown. Concomitant medications: unknown. Troglitazone therapy started on unknown date. Hospitalized with sepsis, transplanted 26JAN99 for liver failure. No further information available.

LFTs: unknown

34. File MCN # 001-0991-990255 [Transplant]

Fifty-three year old female patient with type 2 diabetes on insulin. Past medical history: hypercholesterolemia. Concomitant medications: diphenhydramine, paracetamol, bismuth salicylate. Troglitazone 400mg/day started 04NOV98. Normal lab values found on 04NOV98 and 30NOV 98. During DEC98 the patient reported nausea, dark urine, yellow skin. Troglitazone discontinued on 14JAN99. On 27JAN99 patient presented with jaundice; AST/ALT were 2116 and 2244 units, respectively, and total bilirubin was 22.2 mg/dL. Hepatitis A IgG positive. On 28JAN99 liver biopsy was performed: ballooning degeneration and hepatocytes necrosis; sections with disruption of the lobular architecture; portal tracts with mild mixed inflammatory infiltrate composed of lymphocytes, neutrophils and plasma cells. On 31JAN99: AST/ALT of 1812 and 1526 units, respectively. On 02FEB99: AST/ALT of 1936 and 1675 units, respectively and total bilirubin of 22.9 mg/dL. Hepatitis B core antibody positive; hepatitis B surface antigen positive; CMV positive. Second liver biopsy on 02FEB99: diffuse non-confluent hepatic necrosis with irregular fibrosis and bile duct proliferation. Patient underwent liver transplant on 23FEB99.

LFTs: 11/04/98: AST=23; total bili=0.5
 11/30/98: ALT normal; AST normal
 01/--/99: ALT=2000; AST=2000; total bili=26.0
 01/27/99: ALT=2244; AST=2116; total bili=22.2
 01/29/99: ALT=1475; AST=1678; total bili=19.8
 01/30/99: AST=1872; total bili=20.2
 01/31/99: ALT=1526; AST=1812; total bili=20.5
 02/01/99: ALT=1287; AST=1588 and 1901; total bili=20.4
 02/02/99: ALT=1675; AST=1936; direct/total bili=14.1/22.9
 02/03/99: ALT=1542; AST=1746; total bili=25.2
 02/04/99: ALT=1390; AST=1729; total bili=28.0
 02/05/99: ALT=1241; AST=1507; total bili=24.0

02/06/99: ALT=1203; AST=1444; total bili=24.7
02/07/99: ALT=1089; AST=1428; total bili=24.1
02/08/99: ALT=1206; AST=1450; total bili=28.0

35. File MCN# 001-0991-990274

Sixty-eight year old female, type 2 diabetic. Past medical history: elevated LFT's while on Lopid in 1988; hypothyroid; hypertension, CABG, hypercholesterolemia. Concomitant medications: simvastatin, levothyroxine, atenolol, estradiol. Troglitazone started 1JAN98, discontinued 1AUG98. Had "fulminant hepatic failure" 1AUG98; liver biopsy showed "patchy hepatitis with cirrhosis." ANA positive; Antimicrosomal AB positive. Initially improved, then deteriorated, evaluated for liver transplant. Developed rash, mentation worsened, had GI bleed, died 28SEP98. Autopsy: "massive subtotal hepatic necrosis with early micronodular cirrhosis".

LFTs: 08/07/98: AST=1245; total bili=10.3
09/16/98: ALT=68; AST=78; total bili=18.8 and 18.2

United States Non-Death/Non-Transplant Cases

36. File MCN # 001-0991-970964

Sixty-three year old male with diabetes on insulin. Past medical history: multiple diabetic complications, fatty liver, hypothyroidism, heart/vascular disease, family history of lupus. Concomitant medications: lovastatin, atorvastatin, fosinopril, glibenclamide. Troglitazone 200 mg/day initiated on 09APR97, increased to 400 mg/day in MAY97. On 04SEP97 the patient presented with jaundice and hepatosplenomegaly. Troglitazone discontinued on 09SEP97. Lab tests on 11SEP97 indicated AST/ALT of 1496 and 860 units, respectively, and total bilirubin of 5.9 mg/dL. The patient was negative for hepatitis B and C. Liver biopsy on 18SEP97: pronounced subacute hepatitis including hydropic degeneration, acidophilic bodies, lymphoplasmacytic infiltrates, areas of bridging necrosis, occasional eosinophils. Further lab tests were carried out on: NOV97: AST/ALT of 165 and 117 units, respectively, and total bilirubin 7.25 mg/dL; 25FEB98: AST/ALT of 65 and 60 units, respectively, and total bilirubin 1.73 mg/dL; 25MAR98: AST/ALT of 68 and 56 units, respectively and total bilirubin 1.3 mg/dL: in this date, positive anti-nuclear antibody titer and borderline mitochondrial antibody titer. On 10SEP98, transaminases and bilirubin values were back to the normal range. Abdominal ultrasound on 18SEP98 indicated evidence of cirrhosis.

LFTs: 09/11/97:	ALT=1496; AST=860; total bili=5.9
09/20/97:	ALT=1417; AST=775; total bili=7.8
11/06/97:	ALT=165; AST=117; direct/total bili=1.99/7.25
12/26/97:	ALT=79; AST=86; total bili=6.5
01/07/98:	ALT=58; AST=53; total bili=4.32
02/25/98:	ALT=65; AST=60; total bili=1.73
03/25/98:	ALT=68; AST=56; total bili=1.3
05/14/98:	ALT=35; AST=42; total bili=1.6
09/10/98:	ALT=47; AST=33; total bili=0.9
11/09/98:	ALT=22; AST=28; total bili=0.81

37. File MCN # 001-0991-971222

Eighty year old female patient with diabetes. Past medical history: none mentioned. Concomitant medications: many (unspecified). The patient started troglitazone; subsequently she developed cardiac arrest, was resuscitated and hospitalized: in ICU she experienced confusion and her bilirubin was found at 18 mg/dL. Troglitazone discontinued on NOV97 after two weeks of use. Jaundice did not improve upon troglitazone discontinuation and liver biopsy indicated hepatitis.

LFTs: date unknown: total bili=18

38. File MCN # 001-0991-980697

Forty-three year old female patient with type 2 diabetes on insulin. Past medical history: hypertension and diabetic peripheral neuropathy. Concomitant medications: benazepril. Troglitazone started on 12OCT97 at 200 mg/day, increased on 24OCT97 at 400 mg/day. On 30MAR98 altered liver function tests: AST/ALT 720 and 536 units, respectively, and total bilirubin 16.6 mg/dL. Negative for hepatitis A, B, C. Troglitazone discontinued. Patient followed-up on outpatient basis. On 08APR98 hospitalization for "third spacing"; total bilirubin reported in "mid 19's" during hospitalization. On 14APR98 patient discharged in stable condition but on 23APR98 readmitted to hospital with diagnosis of hepatic encephalopathy and urinary tract infection. On 27APR98 the patient had not yet recovered; she was again managed on outpatient basis and was still being treated for urinary tract infection. Total bilirubin "in the 3's"; ammonia "in the 70's" while on lactulose.

LFTs: 03/30/98: ALT=536; AST=720; direct/total bili=9.97/16.6
04/08/98: total bili=mid 19

39. File MCN # 001-0991-981123

Forty-seven year old man with newly diagnosed type 2 diabetes. Medical history: heavy alcohol user in the past. Concomitant medications: allopurinol, given for several months to one year. Troglitazone 400 mg/day initiated on 01MAY98. On 02MAY98 patient complained of nausea and on 04MAY98 developed vomiting. On that date troglitazone was discontinued. The day after the patient continued to vomit and reported dark urine. On 07MAY98 AST/ALT were found over 1400 and 3300 units, respectively. On 20MAY98 AST/ALT were decreased to 1400 and 700 units, respectively. The patient was still vomiting. Liver biopsy on 27MAY98 indicated hepatocellular necrosis and inflammatory infiltrates composed of lymphocytes, plasma cells, polymorphic leukocytes and eosinophils. Serologies were highly positive for Epstein-Barr virus IgG and positive for anti-hepatitis B surface antigen. By 28JUL98 the patient had completely recovered and AST/ALT values were back to the normal range.

LFTs: 05/07/98: ALT over 3300; AST over 1400
05/20/98: ALT=1400; AST=700; total bili=13.0
05/27/98: ALT=1950; AST=1040; direct/total bili=8.5/15.0
06/29/98: ALT=600; AST=237; total bili=4.4
07/08/98: ALT=34; AST=60; total bili=1.3
07/28/98: ALT "normal"; AST "normal"; total bili=0.4

40. File MCN # 001-0991-981684

Seventy-eight year old female patient with type 2 diabetes. Past medical history: hypertension, hyperlipidemia, renal insufficiency. Concomitant medications: glipizide, pravastatin. In 1998 the patient experienced jaundice after about one month of therapy with troglitazone, 400 mg/day. On unspecified dates patient was hospitalized, total

bilirubin 17-18 mg/dL and elevated LFTs (values unspecified); troglitazone stopped. Last follow up from the physician on 24SEP98 indicates that the patient is still hospitalized, developed ascites and has a bilirubin of 9 mg/dL. Information from the MedWatch CTU program on 28OCT98 indicates liver failure in JUL98.

LFTs: exact dates and values unknown

41. File MCN # 001-0991-982320

Fifty-two year old male patient with type 2 diabetes. Past medical history: hypertension, coronary artery disease, hypercholesterolemia, smoker. Concomitant medications: metoprolol, digoxin, captopril, gemfibrozil, glibenclamide, metformin. Troglitazone started in NOV97 together with glibenclamide and metformin. Routine LFTs (checked on bi-monthly basis) normal. In MAR98 troglitazone and routine liver tests discontinued. Drug resumed on SEP98. On 01DEC98 patient reported nausea, vomiting, dark urine. Troglitazone discontinued on 06DEC98. Total bilirubin 4.3 mg/dL on 08DEC98 and AST/ALT 4960 and 4800 units, respectively, on 09DEC98. Patient improved thereafter but on 12DEC98 acute myocardial infarction was diagnosed. Patient remains hospitalized and LFTs are improved as of 22DEC98 (AST/ALT 46 and 205 units, respectively; total bilirubin 2.3 mg/dL).

LFTs: 12/05/98: ALT=4000; AST=5000; total bili=4.3
12/09/98: ALT=4800; AST=4960; total bili=4.3
12/22/98: ALT=205; AST=46; total bili=2.3

42. File MCN # 001-0991-990129

Fifty-nine year old male patient with diabetes on insulin. No relevant past medical history. Concomitant medications: nizatidine, metoclopramide, ondansetron. Six weeks after starting troglitazone (dose unknown); he was admitted to hospital on 22DEC98 for persistent nausea, vomiting, dark urine; patient had abnormal LFTs (values not given). On 30DEC98 liver biopsy indicated submassive hepatic necrosis with eosinophil infiltration and iron deposition. Troglitazone therapy discontinued. On 05JAN99 patient transferred to other hospital with liver failure. AST/ALT were 534 and 640 units, respectively; total bilirubin 2.8 mg/dL; negative hepatitis B surface Ag; further liver biopsy revealed parenchymal loss. AST/ALT values on 11JAN99 were 285 and 372 units, respectively, and the patient was discharged in stable condition. The patient was improving thereafter and LFTs improved as well:

on 21JAN99 AST/ALT were 260 and 264 units, respectively; total bilirubin 2.5 mg/dL;
on 11FEB99 AST/ALT were 160 and 152 units, respectively; total bilirubin 2.0 mg/dL;
on 23FEB99 AST/ALT were 101 and 108 units, respectively, total bilirubin 1.7 mg/dL.

LFTs: 01/--/99: ALT=480; AST=370; total bili=2.7
01/05/99: ALT=640; AST=534; direct/total bili=1.2/2.8
01/06/99: ALT=417; AST=324; direct/total bili=1.1/2.5

01/07/99: ALT=377; AST=302; direct/total bili=1.0/2.6
01/08/99: ALT=337; AST=262; direct/total bili=1.0/2.2
01/09/99: ALT=332; AST=272; direct/total bili=1.1/2.4
01/10/99: ALT=308; AST=268; direct/total bili=1.0/2.2
01/11/99: ALT=372 and 312; AST=285 and 280; direct/total bili=1.1 and
1.0/2.3
01/21/99: ALT=264; AST=260 and 267; total bili=2.5
01/25/99: ALT=307; AST=338; total bili=1.9
02/01/99: ALT=279; AST=276; total bili=1.6
02/11/99: ALT=152; AST=160; direct/total bili=0.6/2.0
02/23/99: ALT=108; AST=101; direct/total bili=0.0/1.7

43. File MCN # 001-0991-990167

Seventy-three year old female patient with type 2 diabetes. Past medical history: congestive heart failure, stroke. Concomitant medications: glibenclamide, metformin. Troglitazone 400 mg/day started on JAN99 as replacement for glibenclamide and metformin. Few days later glibenclamide was reintroduced and troglitazone maintained.

Due to hypoglycemic episodes both drugs were discontinued on 21JAN99. LFTs on 22JAN99 were normal. On 24JAN99 patient admitted to hospital (somnolent upon admission is the only information available on the reason for hospitalization) and AST were found to be 900 units, with normal ALT. Amilase: 300. Patient experienced GI bleeding while in hospital. On 26JAN99 AST were decreased to 500 units and the first elevation in ALT was noted (700 IU/L). The patient was more alert but not recovered and remains hospitalized.

LFTs: 01/24/99: ALT normal; AST=900
01/26/98: ALT=700; AST=500

Metformin-Associated Lactic Acidosis (Per 1,000 Patient Years)

Country	Years	Cases	Deaths	Source
Sweden	1972-1981	0.084	0.024	Campbell, 1995
Sweden	1977-1981	0.015	--	Berger, 1995
Sweden	1987-1991	0.024	--	Wilholm & Mynhed, 1993
Switzerland	1972-1977	0.067	--	Wilholm & Mynhed, 1993
United Kingdom	1976-1986	0.027	--	Berger, 1995
Canada	1980-1985	0.18	0.09	Bailey & Natrass, 1988
Conclusion:	0.015-0.18 Cases/1000 Patient Years			Stang, et al; 1997
	0.09-0.024 Deaths/1,000 Patient Years			

New Proposed Use: Troglitazone /Metformin Combination Therapy

1. NEW PROPOSED USE: TROGLITAZONE /METFORMIN COMBINATION THERAPY

In November 1998, an sNDA was submitted to request approval for the use of troglitazone in combination with metformin. This sNDA included the results of 2 clinical studies with troglitazone in combination with metformin or metformin and sulfonylurea. Additional research reports and published literature were also provided to support changes in the Clinical Pharmacology section of the labeling. This sNDA is currently under review.