SLIDES

Epidemiology of Hepatotoxicity with Troglitazone

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Lanh Green, R.Ph., M.P.H.

Office of Postmarketing Drug
Risk Assessment
Center for Drug Evaluation and Research

Background Information on Acute Liver Failure

Classification System for Acute Liver Failure Used by FDA

Hyperacute	0-7 d
Acute	8-28 d
Subacute	29-84 d

Summary of Outcome of Acute Liver Failure from Five Liver Transplant Centers in the US, 1984-1996

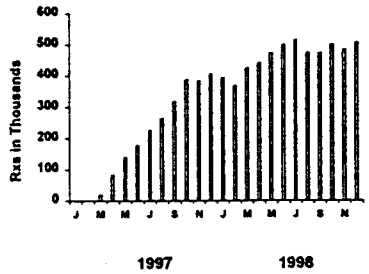
	Number (%)
Alive	
No transplant	50 (23.5)
Transplant	77 (36.2)
Dead	
No transplant	54 (25.4)
Transplant	32 (15.0)

Lack of Association of Diabetes with Acute Liver Failure

- Small ecologic association with chronic liver disease NHDS suggests RR ~ 1.3
- Prevalence of diabetes in patients registered with UNOS for transplant due to acute hepatic necrosis is 4.8%
- Prevalence is no different than that in a general population of similar age, race, and gender
- No association in the literature of DM with acute liver failure

Troglitazone Drug Usage Data

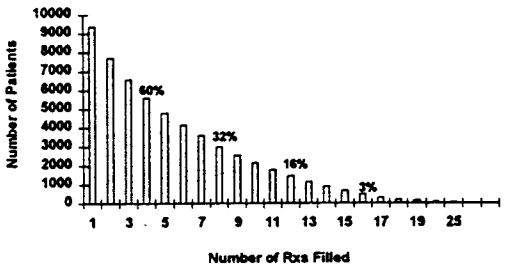
Monthly Prescriptions of Troglitazone in the US, 1997-1998, NPA™ Data



Troglitazone Use in the US, NDTI™, 1997-1998

% Female	43%
Mean Age	60.7
Age Distribution	% Total
0-34	2.2
35-44	8.9
45-54	19.4
55-64	28.3
65+	41.1

Continuation of Troglitazone Use by Patients Treated with the Drug, UHC, 1997-1998



Review of Reported Cases of Acute Liver Failure and Hepatitis with Troglitazone

Definitions Used to Classify Case Reports (1)

- Acute Liver Failure
  - Used classification scheme by O'Grady, et al (UK, 1993)
  - Measured the interval from jaundice onset to encephalopathy/ transplant or death
  - If timing of jaundice unknown, used time of onset of other symptoms, or of stopping troglitazone use

Definitions Used to Classify Case Reports (2)

- Rapid Riser
  - Patient in whom irreversible acute liver failure developed within 37 days of previously normal test results
- Unknown Riser
  - Patient in whom the time course of development of abnormal liver enzymes is unknown

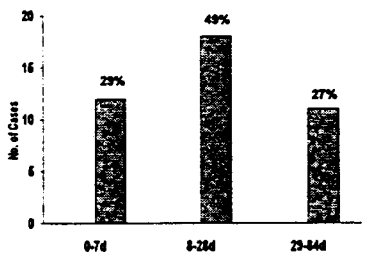
Overview of Cases of Acute Liver Failure and Hepatitis

Acute Liver Failure	43
Probable	38
Possible	5
Hepatitis	81
Hospitalized	46
Not hospitalized	29
Unknown	6

Outcome in 43 Cases of Acute Liver Failure

Alive	12	
No transplant	5	(12.5%)
Transplant	7	(17.5%)
Dead	28	
No Transplant	26	(65%)
Transplant	2	(5%)
Unknown	3	

Time from Jaundice to Encephalopathy in 43 Cases of Acute Liver Failure



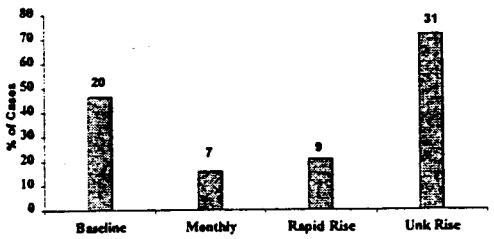
Patient Characteristics in 43 Cases of Acute Liver Failure

Female	70%	
Age	63	(43-91)
Duration of Rx	116 d	(4-236)
Daily dose 200mg	20%	
400mg	69%	
600mg	11%	
Jaundice as 1st Sx	62%	
Jaundice @ Dx	89%	
Time from jaundice to encephalopathy	19 d	(0-70)

First Indication of Hepatic Injury in 43 Cases of Acute Liver Failure

Jaundice	23	(62%)
Other Sxs	9	(24%)
Abnl Enzymes	5	(14%)
Unknown	(6)	

Liver Enzyme Monitoring in 43 Cases of Acute Liver Failure



Time-Course of Liver Enzyme Monitoring in a "Rapid Riser"

	ALT	AST	AlkP	Tbill	
5Feb98	20	19	128		
11Feb98					Began troglit
7Aug98	32	30		0.6	
17Aug98			93	0.6	Some nausea
22Aug98	1670	1688		5.5	Jaundice, hosp
9Sep98					Enceph; intub
10Sep98					Liver tx
12Sep98					Death

Case 14

Time-Course of Liver Enzyme Monitoring in an "Unknown Riser"

	ALT	AST	AlkP	Tbill	
1Dec97					Began troglit
3Dec97	11				"Normal"
1Mar98					Anorexia
4Mar98	252		54	0.5	6xULN; stopped troglit
25Mar98	>1400				Jaundice
15Apr98					Enceph; stage III
18Apr98					Liver tx

Case 15

Observations from Cases of Acute Liver Failure

- Long prescriptions
- Time-lag between blood draw, test-results and communication with patient
- Continuing after onset symptoms (n/v)
- Lack of physician awareness
- Fractionation of patient care

Summary from Review of Acute Liver Failure Cases

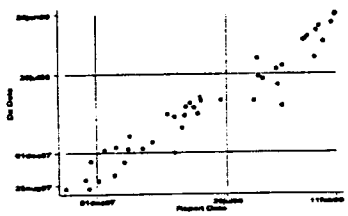
- In 9 of 12 cases with enzyme data (75%), transition from normal to irreversibility occurred within 4 - 34 d
- For most, the time course of liver enzyme change was unknown (n=31)
- The unknown riser with an ALT=252 highlights this issue of irreversibility

Underreporting of Cases

Underreporting of Adverse Drug Reactions From the Literature

Country	Drug	Reaction	Reporting Rate
UK	Practolol	Oculocutaneous syn	<< 2%
UK	NSAIDS	Aplastic anemia	11%
UK	OC's	TE death in women	15%
US	Digitalis	Hosp for toxicity	0.3%
US	Isoniazid	Fatal hepatitis	10%
US	DTP	SIDS	10-20%
US	RI survey	Serious	<< 3%
US	MD survey	Medically serious	< 8-13%

Reporting Over Time of Acute Liver Failure with Troglitazone



Modeling of Risk and Hazard Rates for Acute Liver Failure with Troglitazone

Methods Used to Estimate the Risk of Acute Liver Failure with Troglitazone

- Standard life-table analysis
- Pattern of troglitazone usage from UHC database used to estimate national pattern
- Rate of reported acute liver failure calculated for each separate month of drug usage (interval-specific hazard rate)

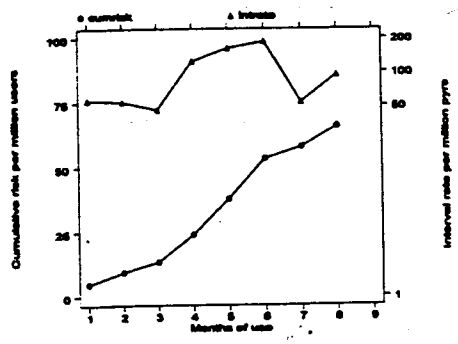
Life-Table Analysis of Risk of Acute Liver Failure Based on Reported Cases from an Estimated Population of 1.23 Million Users, 1997-1998

Months of Use	Interval Specific Hazard Rate per 10^6 pyrs	Cumulative Risk (1 per "X" Users)
1	56	209,158
2	54	107,003
3	46	75,182
4	124	41,895
5	162	26,556
6	185	18,723
7	54	17,250
8	94	15,154

Cumulative Risk of Acute Liver Failure Adjusted for Underreporting*

Duration of Use	Level of Underreporting 25%	10%	5%
1 mos	52,290	20,916	10,458
3 mos	18,796	7,518	3,759
6 mos	4,681	1,872	936
8 mos	3,789	1,515	758

*Risk shown as 1 per "X" troglitazone users



Population-Based Estimates of the Rate of Acute Liver failure with Troglitazone

Epidemiologic Studies Providing Population-Based Estimates of Acute Liver Failure

Country	Source	Years	Person-Years	Rate per 10^6 Person Years (95% CI)
U.S.	Medicaid	1980-87	9.8×10^6	0.8 (0.3 – 1.8)
U.S.	HMO	1977-81	1.4×10^6	0 (0 – 2.6)
Canada	Saskatch	1982-86	0.47×10^6	0 (0 – 6.4)
U.K.	GPRD	1987-91	0.26×10^6	0 (0 – 11.7)
U.K.	GPRD	1990-93	0.18×10^6	0 (0.6 – 16.6)
			12.11×10^6	0.6 (0.2 – 1.3)

Summary of Population Based Data on Risk of Acute Liver Failure with Troglitazone

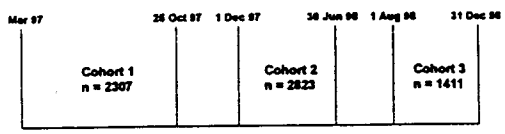
Study	No.	≥ 6 mos Rx	Pyrs	Cases AHF	Incidence Rate per 10^4 pyrs (95% CI)
NDA	2510	45%	1426	0	0 (0-2584)
DPP	585	86%	580	1	1724 (44-9569)
REACH	2433	17% est	785	1	1274 (32-7077)
Glaxo	3034	?	1227	0	0 (0-3002)
Sankyo	1608	?	370	0	0 (0-9920)

Study of Liver Enzyme Monitoring and Severe Liver Injury in Patients Treated with Troglitzone from the United HealthCare Database

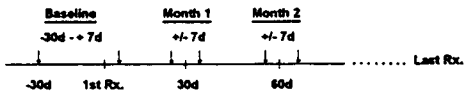
Criteria for Inclusion in the Troglitazone Study Cohort of Liver Enzyme Monitoring

- Enrollment Date ≥ 90 days prior to 1st troglitazone prescription
- Disenrollment or end of study interval occurring prior to anticipated testing time

Overview of Study of Liver Enzyme Monitoring in Troglitazone Users within the United HealthCare Database



Study Design for Measuring Occurrence of Liver Enzyme Monitoring



Size of Troglitazone Monitoring Study Cohort, UHC

Ever received troglitazone	9,369
Total person-years	4,873
≥ 90 day prior enrollment	7,568
Included in enzyme monitoring study	6,541

Liver Enzyme Testing in the Period 30 Days Prior to 7 Days after the First Troglitazone Prescription, by Time Period, UHC

	% with Baseline Test
Cohort 1 (n=2307)	24.5
Cohort 2 (n=2823)	37.0
Cohort 3 (n=1411)	45.1

Full Compliance with Monthly Liver Enzyme Monitoring (+/-7d) by Time Period, in Troglitazone Users, UHC

	Month*					
	1	2	3	4	5	6
Cohort 1	2.6	0.8	0.3	0	0	0
Cohort 2	7.3	2.5	1.0	0.7	0.6	0.8
Cohort 3	9.3	4.2	2.7	0.5		

*Data Shown as Percentage of Eligible Subjects at Each Time Period

Estimated Completeness of Data based on Claims Lag, UHC Enzyme Monitoring Study

Cohort 1	99%
Cohort 2	99%
Cohort 3	>85%

Potential Incidence Rates of Severe Liver Injury in Troglitazone Users, UHC

	n	Incidence Rate per 10^4 pyrs (95% CI)
Possible Acute Liver Failure	3	616 (127-1798)
Possible Hepatitis	4	821 (224-2100)
Total	7	1437 (578-2957)

Other Issues

Registration Rates for Liver Transplantation per 10^9 Prescriptions of Selected Drugs, UNOS, April 1994 - October 1998

Drug Group	No. Registered for LTx	Rxs in Millions	LTx Registration Rate per 10^9 Rxs (95% CI)
Sulfonylureas	0	166.3	0 (0-18)
Metformin	0	40.0	0 (0-75)
Troglitazone	3	7.9	378 (78-1100)
NSAIDS	6	372.1	16 (6-35)
Bromfenac	2	2.6	772 (94-2810)
HMG Co-A	1	206.1	5 (0.1-27)

Lactic Acidosis and Metformin-Diabetes

- Only 2 population-based studies in diabetics:
  - Metformin: 90 per 10^6 pyrs
  - No metformin: 97 per 10^6 pyrs
  - All cases with recognized factors capable of causing LA
- 8.5% of FDA cases free of confounding factors; rate 2 per 10^6 pyrs (Misbin et al. NEJM, 1998)

Summary of Available Data on ADR Fatality Rates with Oral Hypoglycemic Agents

	Death Rate per 10^6 Person-Years
Metformin lactic acidosis	15
Sulfonylurea hypoglycemia	14-33*
Troglitazone acute liver failure	1200-1700

*From Sponsor's briefing document

Underreporting of Severe Liver Injury with Troglitazone based on Obs/Exp Analysis

	Reporting Efficiency	
	Liver Tx/Death	Hospitalized Hepatitis
DPP	1.7-3.0%	
REACH	5.0-8.5%	
UHC	8.4-8.8%	8.3-8.7%
NDA		9.3-9.7%

Benefit and Risk (1)

- Major health benefits will be realized in the future
- Average troglitazone user is 61 years old
- Competing mortality or lack of effectiveness will reduce the pool that can remain on drug long enough to realize major benefits
- Present value of a future health benefit

Benefit and Risk (2)

- Background rate of ALF 1 per 10^6 pyrs
- From multiple population sources:

  DPP: 1724 per 10^6 pyrs (44-9569)

  REACH: 1274 per 10^6 pyrs (32-7077)

  UHC: 616 per 10^6 pyrs (127-1798)
- Life-table analysis adjusted for underreporting suggests risk of ~ 1000 per 10^6 pyrs at 6 mos

Benefit and Risk (3)

- Hazard rate is elevated with first month of use, and peaks at 6 months; then appears to remain high
- Cumulative risk progressively increases with continued exposure
- Most troglitazone users have not yet passed through the period of peak risk

Benefit and Risk (4)

- No obvious predictors of who is at risk
- ALF appears to be unpredictable
- Enzyme monitoring occurs at a low level and in an irregular manner
- No data on the efficacy of monitoring in preventing ALF

Acknowledgements

FDA
Rizwan Ahmad, MD, MPH
Robert Misbin, MD
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UHC
Margaret Burgess
Carol Drinkard, PhD
Stephanie Schech, MPH
Deborah Shatin, PhD

Rezulin®
(Troglitazone) Tablets

Presentation to the
Endocrinologic and Metabolic Drugs
Advisory Committee

Parke-Davis Pharmaceutical Research
March 26, 1999

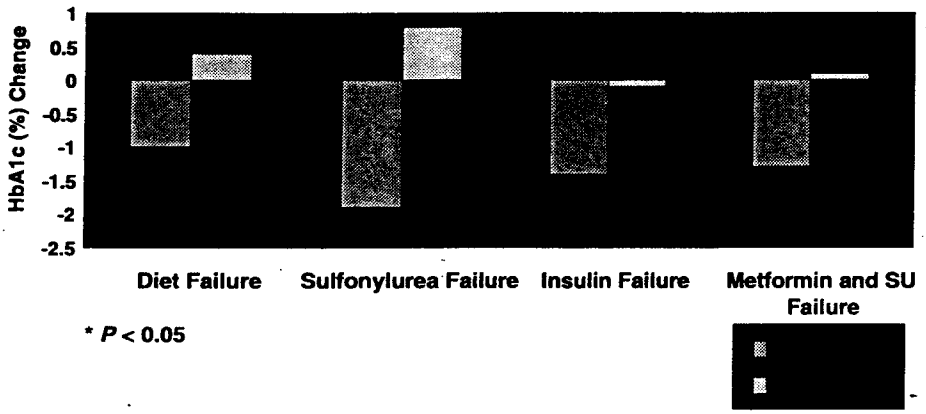
Introduction

Robert Zerbe, MD
Sr. Vice-President, Clinical Research and Development
Parke-Davis

Rezulin® Timeline

• July 1996	Initial NDA Submission (Insulin Combination)
• January 1997	Initial Approval
• February 1997	SNDA Submission (Sulfonylurea Combination, Monotherapy)
• August 1997	SNDA Approval
• November 1998	SNDA Submission (Triple Therapy)

Efficacy of Rezulin



* $P < 0.05$

Labeling Changes Related to Hepatic Failure

October/December 1997

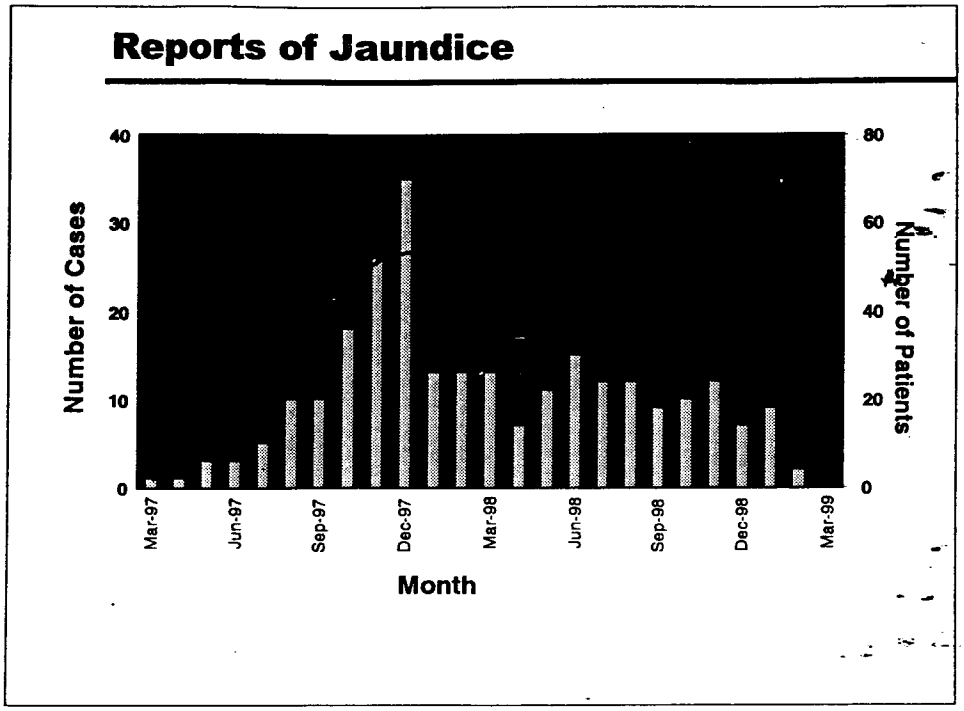
- Boxed Warning
- Routine Monitoring Added
- No therapy if ALT > 3X ULN

July 1998

- Monitoring Extended
- Intensive Follow-up for Mild Elevations
- No therapy if ALT > 1.5 X ULN
- Discontinue monotherapy if no response in two months

Parke-Davis Initiatives

- Better understanding of mechanism and epidemiology
- Better definition of patients who can gain greatest benefit
- Professional education regarding the importance of monitoring


Reports of Jaundice
Number of Cases
Number of Patients
0
10
20
30
40
0
20
40
60
80
Mar-97
Jun-97
Sep-97
Dec-97
Mar-98
Jun-98
Sep-98
Dec-98
Mar-99
Month

Agenda

Introduction	Robert Zerbe, MD
Hepatic Events	Paul Watkins, MD Univ. of Michigan Professor of Medicine and Professor of Pharmacology
Incidence of Serious Liver Events	Mark Pierce, MD, PhD V.P., Clinical Research
	Gerald Faich, MD, MPH President, Pharmaceutical Safety Assessment, Inc.
Comparative Safety of Alternative Therapies	Philip Home, DM, DPhil Univ. of Newcastle, UK Professor of Diabetes Medicine
Lunch	

Agenda (Cont'd.)

Benefits of Rezulin Therapy	Randall Whitcomb, MD V.P., Clinical Research
Risk-Benefit Summary	Robert Zerbe, MD

Key Points

- The risk of liver related death and transplant with Rezulin is low and declining
- The risk compares favorably to the risk of serious events associated with other available treatments
- Physicians have a high awareness of the risk and the need for monitoring
- Rezulin, through it's unique mechanism, provides marked benefit in combination and as monotherapy to hundreds of thousands of patients

Hepatic Events

Paul B. Watkins, MD
Director, General Clinical Research Center
Professor of Medicine
Professor Pharmacology
University of Michigan

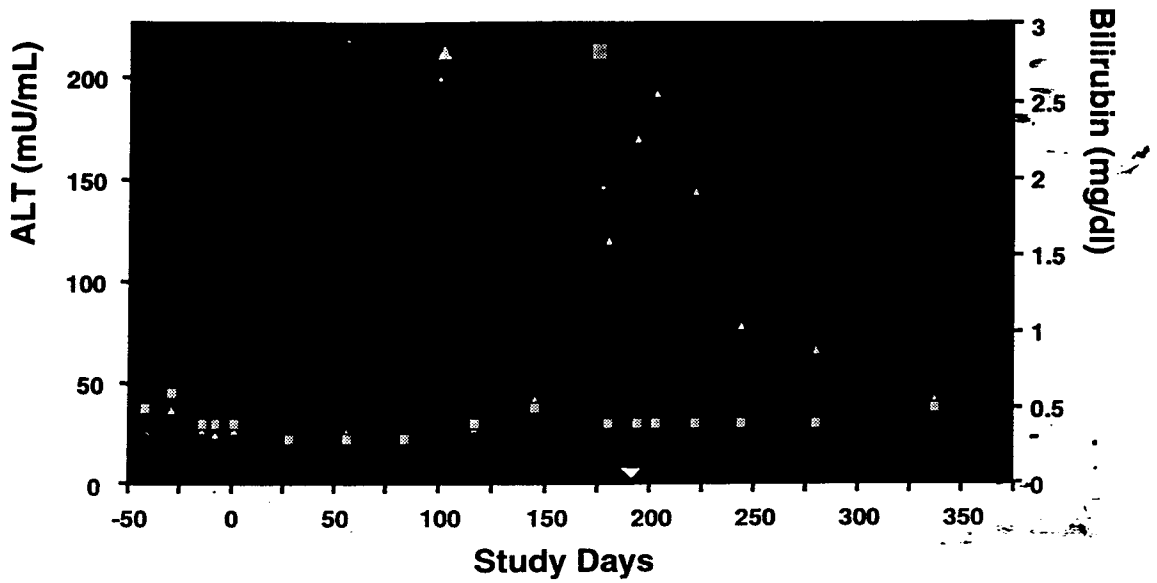
Active Consulting Contracts

- Abbott
- Pfizer
- Roche
- TAP
- Warner-Lambert/Parke-Davis
- FDA

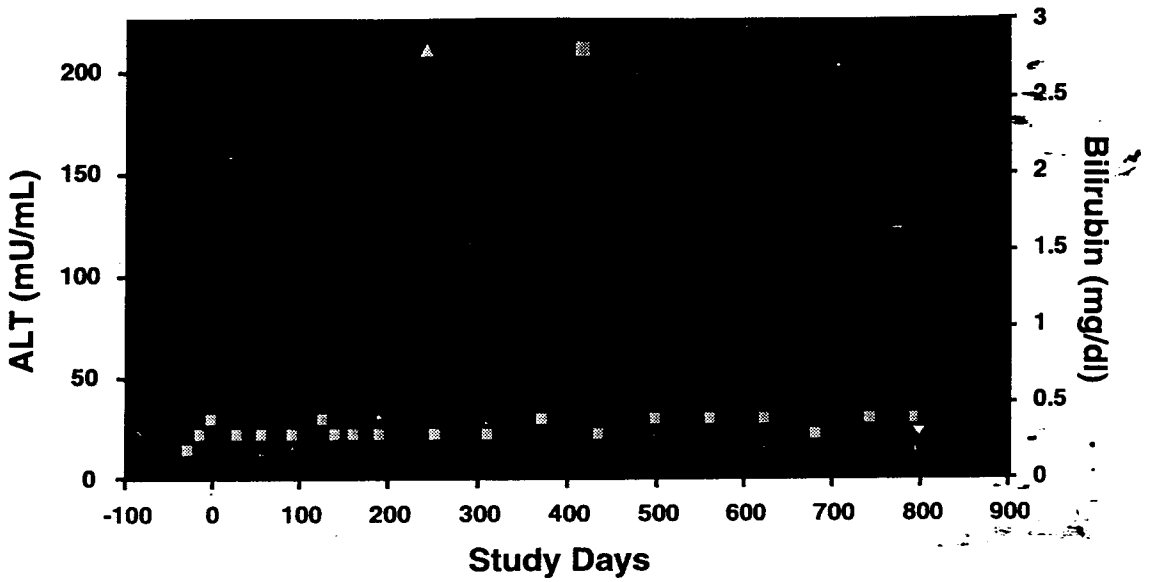
Hepatocellular Injury

- Liver cell is globally injured
- Elevations in serum ALT
- Height of ALT correlates with extent of injury
- ALT > 3x ULN = "Clinically Significant"
- Jaundice = severe injury

Clinical Trial Patient (ALT/Bilirubin)



Clinical Trial Patient (ALT/Bilirubin)



Approach to Review of Spontaneous Cases

- Reviewed all Med Watch liver events on a weekly basis
- Formation of independent review board
- Periodic review of complex cases with other hepatologists

Background Liver Disease in Type 2 Diabetes

- Non-alcoholic steatohepatitis (NASH)
- Hepatitis C

Cases of Acute Liver Failure in 13 US Medical Centers 1994 -1996

	Number	
Acetaminophen overdose	60	20%
Cryptogenic / NANBNC	43	15%
Drug reactions	34	12%
Hepatitis B	30	10%
Hepatitis A	20	7%
Wilson's Disease	19	6%
Autoimmune hepatitis	18	6%
Misc categories	71	24%
Total	295	100%

Liver Transplantation and Surgery, 5:29,1999

Jaundice and Deaths with Hepatocellular Injury

Drug	Jaundice	Death	%	Reference
INH	114	13	12%	Gastroenterology 69:289,1975
Ketoconazole	18	1	6%	Gastroenterology 86:503,1985
Pimoline	43	1	2%	Gastroenterology 99:1517,1990
Diclofenac	90	7	7%	Hepatology 22:820,1995

U.S. Reports of Jaundice in Rezulin Treated Patients

Total number of cases	290
Unlikely / unrelated	96
Probable / Possible / Insufficient data	194
Predicted deaths	~ 20

As of 3/5/99.

US Deaths/ Transplants

Total # of reported cases	75	
Probable	16	28
Possible	12	

Confounding Factors in the 28 Probable/Possible Deaths/Transplants

Preexisting liver disease		7
Hepatitis B -	3	
Cirrhosis -	2	
NASH -	1	
CMV -	1	
Known Hepatic Drugs		9
No Factors Present		12

US Deaths/ Transplants

Total # of reported cases	75		
Probable	16	28	40
Possible	12		
Insufficient data	12		
Unlikely/Unrelated	35		

FDA Count Equals 35

In Worldwide Clinical Trials
(n=15,591)

- 2 deaths - "probably related"
- 4 jaundiced patients - ~20 predicted
- Could there have been something unusual about the two patients who died?

Clinical Trial Patient (#1-NIH)

- Flu-like prodrome while ALT < 3x ULN
- CMV IgM antibodies
- Inclusion body observed in liver biopsy
- Necrotic colon discovered at surgery

Letter Dated 6/10/98 to Dr. Genuth

"Conclusion: Accordingly the committee concludes that hepatic necrosis in this case was probably caused by troglitazone and believes that an important contributory role in the fatal outcome may have been played by bowel necrosis, a lesion for which the CMV infection is speculatively incriminable."

Neil Kaplowitz, MD
Professor of Medicine
University of Southern California

Anthony Tavill, MD
Director, Friedman Center
for Digestive and Liver Disorders
Cleveland, Ohio

Hyman J. Zimmerman, MD
Professor of Medicine, Emeritus
George Washington University

Clinical Trial Patient (#2)

- "12 beers daily for 20 years"
- AST > ALT consistent with alcoholic hepatitis
- Height of AST / ALT not consistent
- Liver histology not obtained

Summary of Patient Cases

- Troglitazone contributed to the liver injury in each patient
- Both patients probably had underlying liver disease that reduced the ability to survive the drug related injury

Cases Considered "Rapid Risers"

Mechanisms of Hepatotoxicity Unknown

- No animal or in vitro model available

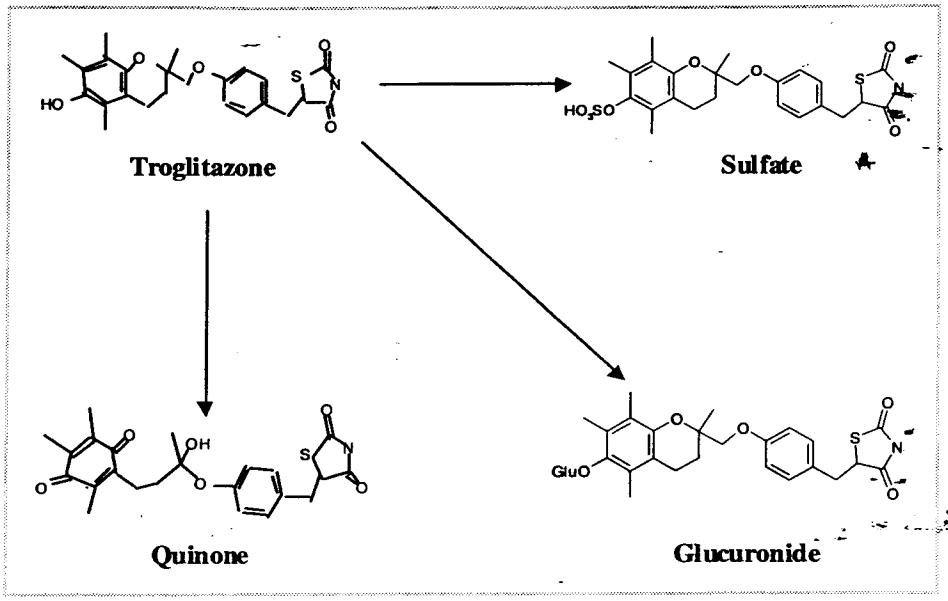
Potential Mechanisms of Hepatotoxicity

Quinone metabolite

CYP3A4 induction

PPARγ activation in liver

Metabolism of Troglitazone



Potential Mechanisms of Hepatotoxicity

Quinone metabolite

CYP3A4 induction

PPARγ activation in liver

Other Drugs Induce CYP3A4

- Rifampin
- Phenytoin
- Carbamazepine
- Glucocorticoids

Potential Mechanisms of Hepatotoxicity

Quinone metabolite

CYP3A4 induction

PPARγ activation in liver

Conclusions

- Acute Liver Failure due to troglitazone is rare and idiosyncratic
- Assessment of many cases is not straightforward
- The agreed number of U.S. reported deaths / transplants due to drug is 35
- The mechanisms involved in troglitazone hepatotoxicity are unknown

Incidence of Serious Liver Events

Mark Pierce, MD, PhD

Vice President, Clinical Research
Parke-Davis Pharmaceutical Research

Outline of Presentation

- Incidence in clinical trials
- Incidence for marketed drug
  - Overall
  - By labeling change
  - By duration of therapy

Worldwide Clinical Trial Data

Sponsor	# Pts. Exposed	Jaundice	Hepatic Death
Parke-Davis	7,656	3	1
NIH	585	1	1
Sankyo	4,147	0	0
GlaxoWellcome	3,203	0	0
TOTAL	15,591	4	2*

Incidence Rate of a Fatal Liver Event = 1 in 7,800

95% CI: 1 in 2,200 - 1 in 62,900

*These patients were also jaundiced.

Overall Post-Marketing Reporting Rate

March 1997–March 1999

35 in 1.58 million = 1 in 45,098

Factors Increasing Reporting Rates for Adverse Events

	Rezulin
Newness[1,2,3,4]	✓
Severity[1,5,6,7,2,8]	✓
Clarity of signal[9]	✓

1. Milstien JB, et al. *Drug Information J.* 1986;20:157.
2. Lumley CE et al. *Pharmaceut Med.* 1986;1:205.
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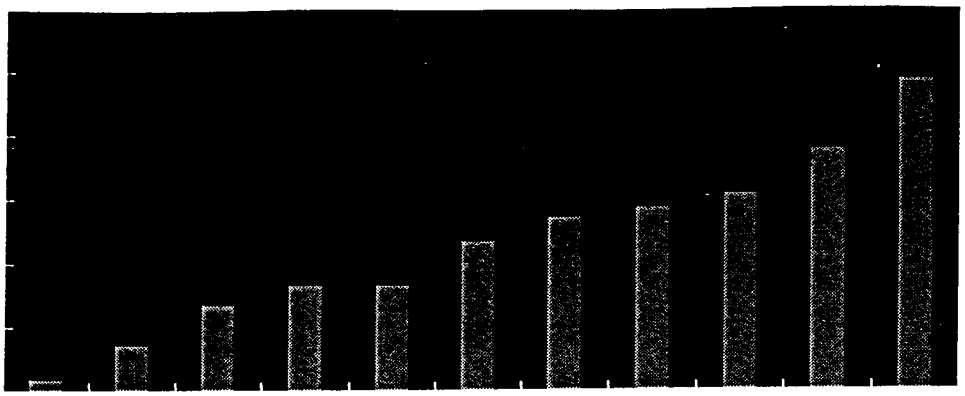
9. Koch-Weser J. *NEJM.* 1969;280:20.

Trend in Post-Marketing Reports
(All Drugs)



Factors Increasing Reporting Rates for Adverse Events

	Rezulin
Newness[1,2,3,4]	✓
Severity[1,5,6,7,2,8]	✓
Clarity of signal[9]	✓
Secular trend[5,3,6,10,11]	✓
Active monitoring	✓

1. Milstien JB, et al. *Drug Information J.* 1986;20:157.
2. Lumley CE et al. *Pharmaceut Med.* 1986;1:205.
3. Faich GA, et al. *JAMA.* 1987;257:2068.
4. Sachs RM, Bortnichak EA. *Am J Med.* 1987;81:49.
5. Faich GA, et al. *Arch Intern Med.* 1998;148:758.
6. Piazza Hepp TD, Kennedy DL. *Am J Health-Syst Pharm.* 1995;52:1436.
7. Bergman U, et al. *Brit Med J.* 1978;2:464.
8. Rogers AM, et al. *Arch Intern Med.* 1988;148:1596.
9. Koch-Weser J. *NEJM.* 1969;280:20.
10. Scott HD, et al. *JAMA.* 1990;263:1785.
11. Burke LB, et al. Chapter 9. In: *Pharmacoepidemiology An Introduction*, 3rd Edition, AG Harzema, et al. ed. Cincinnati: Whitney Books Company, 1998.

Factors Increasing Reporting Rates for Adverse Events

	Rezulin
Newness[1,2,3,4]	✓
Severity[1,5,6,7,2,8]	✓
Clarity of signal[9]	✓
Secular trend[5,3,6,10,11]	✓
Active monitoring	✓
Sales representative contacts	✓

1. Milstien JB, et al. *Drug Information J.* 1986;20:157.
2. Lumley CE et al. *Pharmaceut Med.* 1986;1:205.
3. Faich GA, et al. *JAMA.* 1987;257:2068.
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Active monitoring	✓
Sales representative contacts	✓
Publicity[1,2,3]	✓

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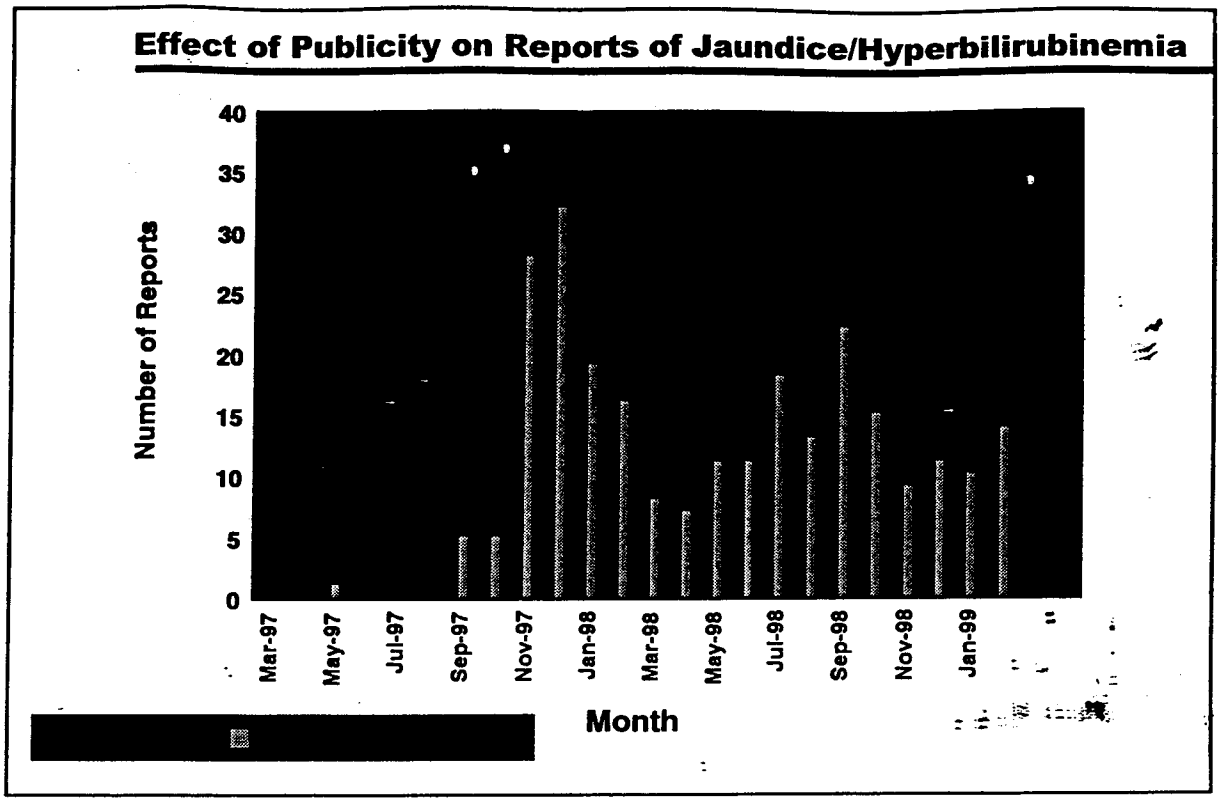
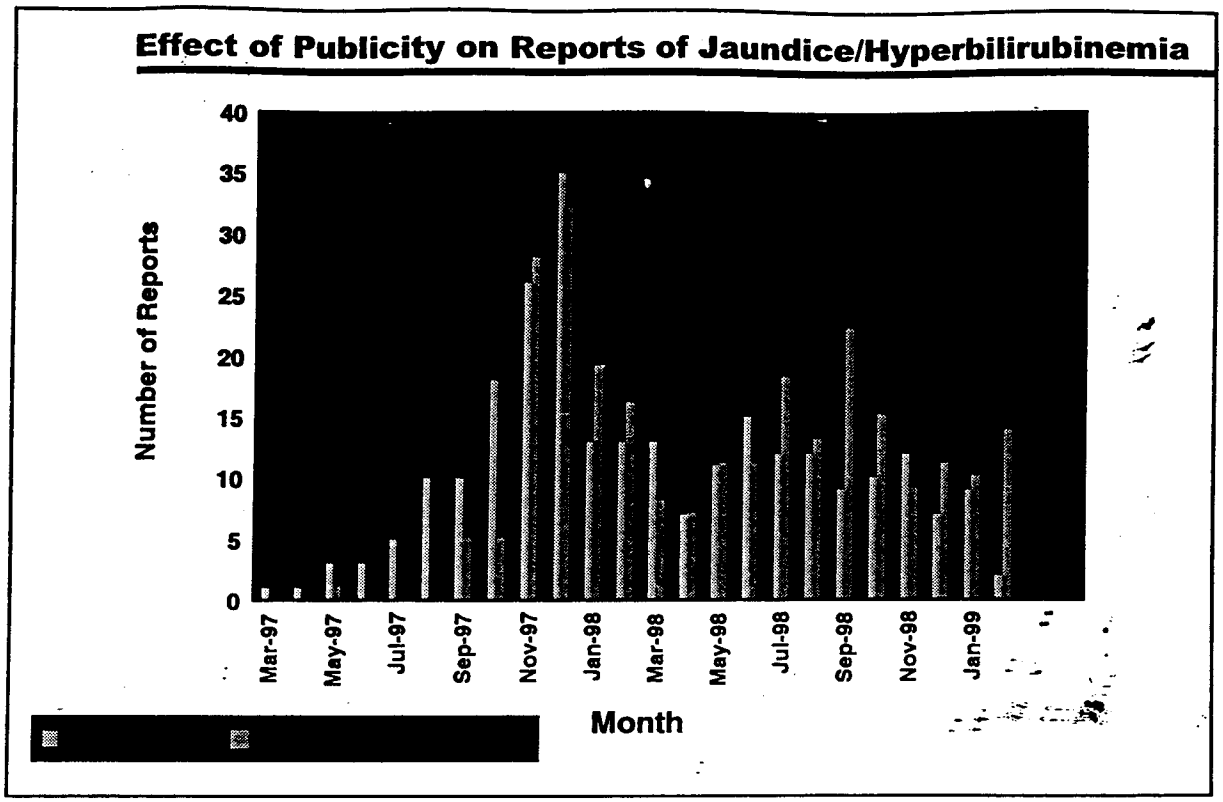
13. Rawlins MD. *Brit J Clin Pharmac.* 1988;26:1.
14. Rossi AC, et al. *JAMA.* 1988;259:1203.


Effect of Publicity on Reports of Jaundice/Hyperbilirubinemia
Number of Reports
40
35
30
25
20
15
10
5
0
Mar-97
May-97
Jul-97
Sep-97
Nov-97
Jan-98
Mar-98
May-98
Jul-98
Sep-98
Nov-98
Jan-99
Month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Mar-98
May-98
Jul-98
Sep-98
Nov-98
Jan-99
Month

Reporting of Liver Transplants
1998

United Network for Organ Sharing

- 4,394 transplants
- 4 transplants involved patients taking Rezulin
- Each transplant was reported to Parke-Davis and the FDA

Conclusion

- No evidence of unreported transplants

Survey of Physicians Treating Patients with Type 2 Diabetes

Methods

- AE reporting and safety monitoring of patients with Type 2 diabetes receiving oral hypoglycemic drugs
- 600 physicians surveyed
  - Randomly selected
  - Proportion in each specialty matched prescriber mix
- Anonymity

Survey of Physicians Treating Patients with Type 2 Diabetes

Adverse Event	% Likelihood of Report
Liver failure leading to death or transplant	92
Lactic acidosis leading to death	90
Jaundice	61
Lactic acidosis with full recovery	58
Reversible Liver Dysfunction	49
Hypoglycemia	17

Survey of Physicians Treating Patients with Type 2 Diabetes

LFT monitoring awareness

- 96% of physicians were aware of the need for LFT monitoring

LFT monitoring compliance

- 97% of patients receive baseline LFTs
- 82% of patients receive monthly X 8 LFTs

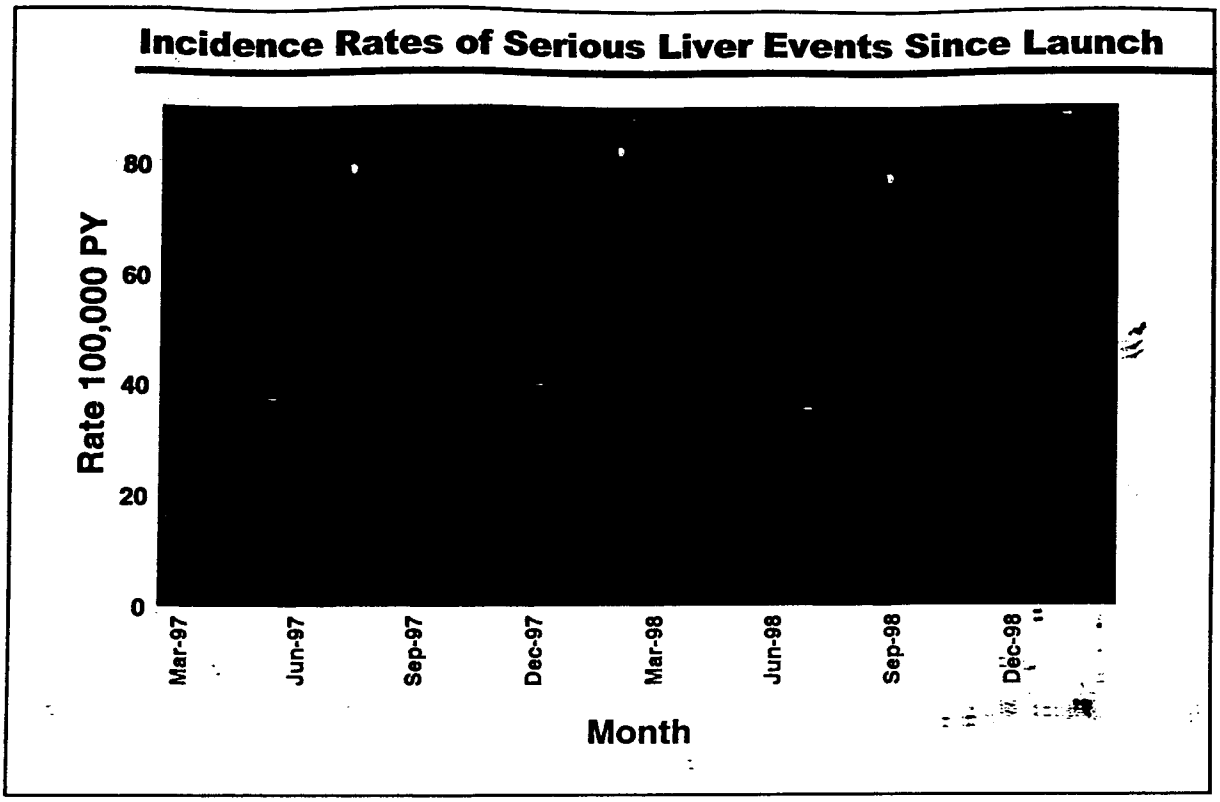
Issues With Claims Data

UHC Study

- Claims data often missing
- Claims sometimes not submitted
- Long delays in claim receipt

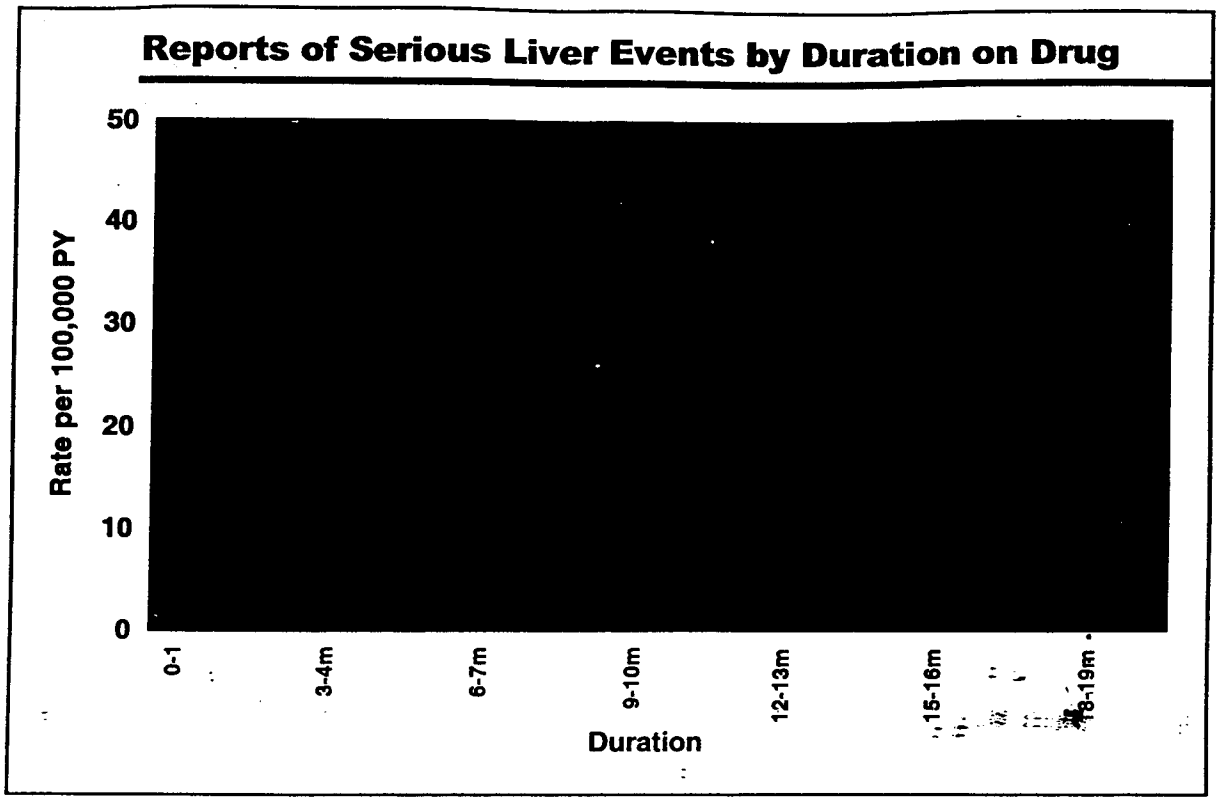
Conclusions

- Claims data are unreliable
- Data do not reflect absolute level of monitoring
- Data do show 2-3 X increase in monitoring frequency


Incidence Rates of Serious Liver Events Since Launch
Rate 100,000 PY
80
60
40
20
0
Mar-97
Jun-97
Sep-97
Dec-97
Mar-98
Jun-98
Sep-98
Dec-98
Month

Effect of Labeling Changes

Year	Cases	New Users	Rate
1997	20	726,570	1 in 36,329
1998-99	15	851,883	1 in 56,792


Reports of Serious Liver Events by Duration on Drug
Rate per 100,000 PY
50
40
30
20
10
0
0-1
3-4m
6-7m
9-10m
12-13m
15-16m
18-19m
Duration

Conclusions Regarding Incidence

- The incidence of liver-related death and transplant is low
- The risk of jaundice and death due to liver failure or transplant substantially declines after 6-8 months of therapy
- The reported rate of adverse liver events has decreased following labeling changes