1449

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Joan Claybrook, President

July 27, 1998

Michael Friedman, M.D.
Lead Deputy Commissioner,
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Friedman,

We have obtained information from the FDA that as of June 5, 1998, there had been at least 21 deaths from liver failure and three patients requiring liver transplants caused by the recently-approved diabetes drug, troglitazone (Rezulin-Parke-Davis/Warner Lambert). In addition, there have been more than 100 patients hospitalized with liver toxicity caused by the drug. Since June 5th, there have been at least five additional deaths from liver damage associated with the use of this drug reported to the FDA for a total of at least 26 deaths from liver failure. The total number of reports received by the FDA in which liver toxicity was associated with troglitazone is more than 560 since March, 1997, when the drug was first marketed. Given that it is estimated that only about one in ten adverse reactions which occur are reported to the FDA, it is likely that there may be as many as 200 deaths from liver damage which have actually occurred. Public Citizen's Health Research Group hereby petitions the FDA pursuant to 21 CFR, section 10.30 to initiate action to ban troglitazone as authorized by 21 U.S.C., section 355 (e) of the Federal Food, Drug and Cosmetic Act because earlier attempts to prevent its liver-damaging toxicity have failed.

The inadequate response to this latest information about the deaths caused by troglitazone--another warning letter planned for this week from Parke-Davis to doctors and minor changes in the labeling agreed upon by the company and the FDA (see attached chronology)--are doomed to the same failure as the previous, similar warning efforts with the drug. In addition, Duract, a painkiller approved in 1996, was recently banned after four patients had died of liver damage and eight patients had required liver transplants. A boxed warning label, advising how to "safely" use the drug had been added in February, 1998, but was not effective and, after additional patients had died of liver damage, the drug was banned in June of this year.

Ralph Nader, Founder

1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000

In December, 1997, based on 130 worldwide cases of liver damage linked to troglitazone, including six deaths, the British government concluded that **"the risks of troglitazone therapy outweigh the potential benefits"** and the drug was withdrawn from the UK. The British government added that **"at present, no clear risk factors for the development of hepatic reactions have been identified which might allow the drug to be used safely in some patients."** Glaxo-Wellcome, which had been marketing the drug in the UK, also withdrew license applications for troglitazone under the European Commission's "mutual recognition" process and all other regulatory activity for the drug on Glaxo's part has also been suspended.

Instead of withdrawing the drug in the United States, the FDA, in December, 1997, increased the amount of monitoring of patients for liver damage (blood tests to detect this) to ten times in the first year of use from the previous five times which had been in effect for a month. Almost all of the deaths from liver toxicity have occurred after the latest (December 1, 1997) label change (which included a boxed warning) was made, reflecting the fact that the warnings are clearly inadequate to prevent the increasing amount of serious, often fatal liver damage occurring in patients using troglitazone. As of now, this drug is only available in the United States and Japan, all other countries and one of its developers, Glaxo-Wellcome, being too concerned to allow such a dangerous drug to be marketed.

History of Knowledge of Liver Toxicity (see attached chronology)

Before troglitazone was approved, 1.9% of patients in clinical trials getting the drug had abnormal liver tests (three or more times normal) compared with 0.6% of placebo-treated patients. Twenty patients treated with the drug (out of 2510) were withdrawn from treatment because of abnormal liver tests. During the December, 1996 FDA advisory committee meeting which recommended approving troglitazone, concern about the drug concentrating in the liver (30 times the concentration in plasma, in rats) was expressed by the FDA. It was stated that "at least in rats we have reason to be concerned about what might happen ultimately in liver, a target tissue." When the drug was first approved, however, there was no recommendation for monitoring of liver function, only a precaution with the above information about abnormal liver tests in people during the trials.

Several months after the marketing launch of troglitazone in March, 1997, some cases of liver damage began to be reported and by October 28, 1997, there were 35 post-marketing reports of liver injury including 2 cases of liver failure, one resulting in a death, one in a transplant. The FDA-Parke-Davis response to this was to add a non-boxed warning to the label about "rare" cases of liver failure and to recommend that liver tests on patients using the drug be done five times during the first year of use. A "Dear Doctor" letter was sent on October 28, 1997.

As mentioned above, by December, 1997 there had been 130 cases of liver toxicity including six deaths worldwide and the drug was withdrawn from the market in the U.K. A boxed warning was added to the label in the U.S. and the frequency of liver tests was increased to 10 times in the first year of use of the drug. Another "Dear Doctor" letter was sent by Parke-Davis to U.S. doctors on December 1, 1997.

In June, 1998, because of a death in a patient in an NIH-sponsored study using troglitazone who had developed liver failure, the treatment arm of the study which involved the use of the drug was canceled.

This study was examining the possibility that drugs such as troglitazone could prevent the development of diabetes. The patient who died was one of 585 patients getting troglitazone in the study.

Now, in the face of at least 25 deaths from liver failure and 3 additional patients requiring liver transplant, the frequency of liver tests has been increased to 11 times during the first year of use. Additional changes in the label include repeating liver tests if results show 1.5 to 2 times elevation above normal and stopping the drug after two months, if it is being used as the sole treatment for diabetes and it has not been found effective by then. Another "Dear Doctor" letter is being sent.

There is little question that the newest round of label changes will be as ineffective as the previous ones in stemming the rapidly-rising number of deaths from liver failure in patients using troglitazone. It is unfortunate that the recent case of Duract, in which warning labels similarly failed to prevent fatal cases of liver damage and the drug had to be banned to protect the American public, has not led to the ban of troglitazone in this country, a ban which has now been in effect for almost eight months in the United Kingdom. How many more Americans will have to die or require liver transplants before Parke-Davis and the FDA take action to protect people in this country by banning the drug?

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

We look forward to a prompt response to this petition.

Sincerely,

Sidney M. Wolfe, M.D.
Director, Public Citizen's Health Research Group

Larry Sasich, Pharm. D., M.P.H.
Research Associate, Public Citizen's Health Research Group

TROGLITAZONE (REZULIN) CHRONOLOGY

DATE	EVENT
December 11, 1996 Advisory Committee Meeting	Endocrinologic and Metabolic Drugs Advisory Committee#65 Bone: "To summarize then, with regard to the indication of troglitazone for the treatment of Type II diabetes in conjunction with insulin, the committee has voted eight to nothing, right, that the study designs and efficacy endpoints and other information presented, taken together, are adequate to assess the efficacy and safety of this drug for the proposed patient population, which we have described several times now."
January 1997 Approved	Rezulin is indicated for use in patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA_{1c} > 8.5%) despite insulin therapy of over 30 units per day as multiple injections. PRECAUTIONS 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 which were consistent with an idiosyncratic drug reaction.[1] NO RECOMMENDATION FOR LIVER FUNCTION MONITORING
August 4, 1997	Supplemental approval for use in combination with sulfonylureas in the treatment of type II diabetes and as monotherapy in type II diabetes.
October 28, 1997	Dear Healthcare Professional Letter - Labeling Changes WARNINGS Hepatic RARE CASES OF SEVERE IDIOSYNCRATIC HEPATOCELLULAR INJURY HAVE BEEN REPORTED DURING MARKETED USE. THE HEPATIC INJURY IS USUALLY REVERSIBLE, BUT VERY RARE CASES OF HEPATIC FAILURE, INCLUDING DEATH, HAVE BEEN REPORTED. INJURY HAS OCCURRED AFTER BOTH SHORT- AND LONG-TERM TREATMENT. 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.[2] LIVER MONITORING: 5 TIMES DURING THE FIRST YEAR
November 3, 1997	FDA: As of October 28, 1997, 35 post-marketing reports of liver injury of various degrees have been received. These reports ranged from mildly elevated blood levels of the liver transaminase enzyme to liver failure leading to one liver transplant and one death.[3]

[1]Troglitazone (Rezulin) Professional Product Labeling. *Physicians' Desk Reference 52 ed. 1998* Montvale NJ:Medical Economics Company, Inc.

[2]Dear Healthcare Professional Letter. Important Drug Warning. William R. Sigmund II, M.D., Vice President, Medical and Scientific Affairs, Parke- [2]Davis, October 28, 1997.

[3]Department of Health and Human Services, Food and Drug Administration. FDA Talk Paper: Rezulin Labeling Changes, November 3, 1997.

DATE	EVENT
December 1, 1997	Dear Healthcare Professional Letter Warner-Lambert and the FDA have already completed a thorough review of the worldwide safety experience with Rezulin. On November 3 the FDA asked physicians for reports on additional adverse events. **You will be reassured to know that the additional reports received since early November do not indicate a greater frequency of liver injury or potential for serious harm than had been previously estimated.** This has resulted in a new recommendation that liver enzymes and bilirubin levels of Rezulin-treated patients be measured at the start of therapy and monthly for the first six months of therapy. These tests should then be measured every two months for the remainder of the first year of therapy, and periodically thereafter.[4]
December 1, 1997	Labeling change in the U.S. BOXED WARNING ADDED TO THE BEGINNING OF LABELING Liver enzymes should be measured at the start of therapy, every month for the first six months of treatment, every other month for the next six months, and periodically thereafter. LIVER MONITORING: 10 TIMES IN THE FIRST YEAR "Although FDA will carefully monitor and evaluate reports of liver problems associated with Rezulin, at present the agency continues to find the benefits outweigh the risks for treating appropriately selected and monitored type-2 diabetes patients with Rezulin."[5]
December 1, 1997	Withdrawn from the market in the U.K. "Overall it is considered that, based on present information, the risks of troglitazone therapy outweigh the potential benefits."[6]
December 5, 1997	Glaxo-Wellcome was quoted as saying the withdrawal was warranted because "the reports were coming in so fast and the events were so serious". "We have sufficient patient safety concerns to suspend marketing of the product."[7]
June 4, 1998	The National Institute of Diabetes and Digestive and Kidney Diseases stops testing troglitazone in patients who are at risk of developing diabetes but did not yet have diabetes because of the death of one patient from liver failure.[8]

[4]Dear Healthcare Professional Letter. William R. Sigmund II, M.D., Vice President, Medical and Scientific Affairs, Parke-Davis, December 1, 1997.

[5]Department of Health and Human Services, Food and Drug Administration. FDA Talk Paper: Patient Testing and Labeling Strengthened for Rezulin, December 1, 1997.

[6]Committee on Safety of Medicines. Troglitazone (Romozin) withdrawn. *Current Problems in Pharmacovigilance* 1997;23:13-16.

[7]Troglitazone suspended in U.K. after more adverse events. *Scrip* No. 2290, December 5, 1997, page 15.

[8]National Institute of Diabetes and Digestive and Kidney Diseases News Brief: NIDDK Discontinues Troglitazone Arm of "Diabetes Prevention Program" Clinical Trial. June 4, 1998.

DATE	EVENT
July 27, 1998	NEW LABELING 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, e.g., 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. LIVER MONITORING: 11 TIMES IN THE FIRST YEAR