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Risks of troglitazone apparent before approval in USA

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To the Editor:

I would like to expand on E. Gale's conclusion that the evidence leading to troglitazone's withdrawal in March 2000 'could have been extrapolated from data available in October 1997' [1]. In fact, this evidence had been available to the manufacturer before the drug was approved in the USA in January 1997 and introduced in March 1997.

In a letter to a leading journal in March 1998, Watkins and Whitcomb, representing Parke-Davis, acknowledged publicly for the first time that during the pre-approval clinical trials of troglitazone, 20 patients had developed alanine aminotransferase (ALT) elevations more than ten times the upper limit of normal (ULN) and five additional patients had developed elevations more than 20 times ULN. Similar elevations were not seen with placebo [2]. Unfortunately, the information provided by Watkins and Whitcomb was not entirely accurate. In fact, the five patients with the highest ALT elevations had developed levels more than 30 times ULN, which indicated even more severe hepatic injuries than the elevations described by Watkins and Whitcomb. These events were important signals of potential life-threatening hepatotoxicity, yet although they occurred during the pre-approval trials, information about these severe ALT elevations did not appear in package inserts until June 1999, two and a half years after troglitazone was approved [3].

The early versions of troglitazone product labelling also downplayed the fact that two patients during the pre-approval trials developed jaundice, which was simply

described as 'reversible' [3]. This sounded benign enough. However, drug-induced jaundice is a life-threatening event with a 10% mortality, which the manufacturer understood but did not mention in product labelling [3, 4]. In fact, the occurrence of the two cases of troglitazone-associated jaundice and another case requiring hospitalisation due to hepatic injury, in contrast to no such cases among controls or patients receiving other antidiabetic drugs, raised additional concerns about potential hepatotoxicity with troglitazone. In an analysis of the hepatic events during the Phase 3 clinical trials, Graham et al. of the FDA projected an incidence of acute liver failure with troglitazone of 797 cases per 1 million patient-years. This incidence was more than 240-fold greater than expected in the general population. It was also many times greater than that observed with drugs of known hepatotoxicity such as NSAIDs, amoxicillin/clavulanate, erythromycin and ketoconazole [5].

Professor Gale also concluded: 'Information about the risks of therapy was not freely available to physicians. Too little was released, too late, and false reassurance was repeatedly conveyed'. The findings I have described above demonstrate not only the accuracy of Professor Gale's comment, but also the unmistakable signals of potential life-threatening hepatotoxicity with troglitazone that were available to the manufacturer even before troglitazone was approved in January 1997. Others have commented on this issue, including Kaplowitz and DeLeve, who wrote: 'all of the criteria for a hepatic signal were present at the time of approval of the drug' [6].

If the manufacturer had faithfully conveyed the Phase 3 hepatic events to physicians from the time of troglitazone's introduction in the USA in March 1997, it is possible that many physicians would have employed much greater caution in prescribing troglitazone or avoided prescribing it altogether. Of course, this would have reduced sales, which may explain why such important information was withheld. Regulations and penalties for drug companies that withhold vital safety information from physicians and patients must be strengthened.

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References

1. Gale EAM (2006) Troglitazone: the lesson that nobody learned? *Diabetologia* 49:1–6
2. Watkins PB, Whitcomb RW (1998) Hepatic dysfunction associated with troglitazone. *N Engl J Med* 338:916–917
3. Physicians' desk reference, 52nd and 54th edn. (1998 and 2000) Medical Economics Company, Montvale, New Jersey
4. Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW (1994) Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA* 271:992–998
5. Graham DJ, Drinkard CR, Shatin D (2003) Incidence of idiopathic acute liver failure and hospitalized liver injury in patients treated with troglitazone. *Am J Gastroenterol* 98:175–179
6. Kaplowitz N (2003) Drug-induced liver disorders: introduction and overview. In: Kaplowitz N, DeLeve LD (eds) *Drug-induced liver disease*. Marcel Dekker, New York, pp 1–14