#1485

TROVAN

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Joan Claybrook, President

June 3, 1999

Jane Henney, M.D.
Commissioner, Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

Based on a review of FDA documents, we hereby petition the Food and Drug Administration (FDA) as authorized by 21 U.S.C. , section 355 (e) of the Federal Food, Drug and Cosmetic Act to immediately ban the widely-used antibiotic, TROVAN (trovafloxacin, Pfizer), before more patients die, require a liver transplant or are otherwise injured from liver toxicity caused by this drug. Like two other drugs also approved in 1997, the painkiller Duract (bromfenac) and the diabetes drug Rezulin (troglitazone), there was also clear evidence of liver damage caused by TROVAN (in animals and in humans) before the drug was approved in December 1997. For example, in one study prior to approval in which the drug was used to treat prostatitis, almost 10% of the men (14 out of 140) given the drug developed evidence of liver toxicity (see below). With eight other drugs in the fluoroquinolone family already available in the U.S, as well as dozens of other safer and equally or more effective drugs for infections, the removal of TROVAN from the market will not deprive doctors or patients of a drug which could possibly be considered indispensable. This is yet another instance of a lower standard for approving drugs in recent years than in the past, adding to the toll of Americans killed or seriously injured by drugs which should never have been approved in the first place.

Since February 1998, 140 documented cases of serious liver reactions--largely in the U.S.--have been reported with the use of trovafloxacin. These included eight cases with five deaths and three liver transplants. A spokeswoman for the FDA has said the reports of liver damage were serious, and the Agency is meeting with Pfizer to evaluate the risk.

FDA Pharmacology Review (December 18, 1997)

The FDA knew about liver toxicity with trovafloxacin before approval from animal studies that Public Citizen's Health Research Group obtained from the FDA's pharmacology review of this drug, dated December 18, 1997:

- In a six month rat toxicity study, the FDA pharmacologist reviewing the animal studies found "A dose-related increase in the incidence of minimal to mild 'fatty change' was seen in the livers of male rats from all trovafloxacin groups."[1] This means that there was no safe dose established for this drug in this species.

- In a six month dog toxicity study, hepatocellular vacuolar degeneration and necrosis (direct damage to liver cells) was seen in two of eight dogs at higher doses. Elevated liver enzymes (an indication of liver damage) were seen in both animals.[2]

- In a second six month dog toxicity study, the drug was stopped in three of sixteen dogs because their liver enzymes increased three-fold and biopsies revealed liver changes (necrotizing hepatocellular inflammation). The FDA pharmacologist wrote: "Data from this study indicated that elevation in liver enzymes, especially ALT, accurately predicted the presence of necrotizing inflammation of perivenular hepatocyctes. The necrotic changes were no longer evident approximately 2 months after discontinuation of the drug."[3]

Human Premarketing Studies: NDA Medical Review--December 1997

Background: The Medical Officer (MO) for the drug had been concerned over findings in the two six month dog toxicity studies: increased liver function tests (LFTs) at two months and histologic findings at six months coupled with a small safety factor between human and canine exposure.

Liver adverse events in the clinical trials: In one clinical trial involving 140 patients with prostatitis, lasting 28 days, five patients were discontinued by the investigator for treatment-related increases in liver function transaminases [TAS--a liver test] (values redacted from the FDA document).

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1 Trovafloxacin/alatrofloxacin. *Pharmacology Review* December 18, 1997, p. 42.

2 Ibid, p. 43.

3 Ibid, p. 44.

Ten additional patients had elevations of LFTs ≥3x normal (data redacted). "Despite the fact that the investigators did not consider the LFT abnormalities in the 10 patients as attributable to trovafloxacin, the MO determined that the pattern of the abnormalities was consistent with that of the previously listed 5 patients. . .both in terms of the timing of the events as well as the duration. . . .Therefore, the MO determined that the true incidence of LFT abnormalities (≥3x normal), attributable to the study drug was 14/140 (10%). "[4]

"A trend was observed for liver enzyme elevations after 3 to 4 weeks of trovafloxacin therapy, suggesting that subjects receiving prolonged treatment (≥21 days) may need to have periodic assessment of hepatic function."[5]

Trovafloxacin 200 mg QD was statistically equivalent to ofloxacin 300 mg BID (there was no advantage to trovafloxacin). Fourteen percent of TROVAN patients were discontinued vs 6% of ofloxacin patients.

FDA Safety Update (April to June 1998--after the drug was on the market)

"The MO was of the opinion that trovafloxacin induced a chemical hepatitis (i.e., asymptomatic) after >14 days of therapy. . ."[6]

The April 1998 quarterly report listed 3 cases of increased TAS associated with liver biopsy findings of eosinophilic infiltration of the liver in patients after <14 days therapy.[7]

Of the 11 serious safety reports for liver toxicity, as of June 1998, "the most typical" (MO comment)[8] was a healthy female who developed evidence of an eosinophilic hepatitis with no other obvious etiology.

".... it became apparent that trovafloxacin had the most reported liver-associated AEs [adverse events] within the first 6 months after approval of any of the approved and on the market quinolone antimicrobial agents. Only temofloxacin (withdrawn in 6/92) had a larger number of reported events. [This]. . . serve(s) to illustrate the magnitude of

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4 FDA Medical Officer's Review, December 1997, p. 227.

5 Ibid, p. 228.

6 FDA Medical Officer's Safety Update, August 1998, p. 2.

7 Ibid, p. 2.

8 Ibid, p. 6.

the trovafloxacin-related hepatotoxicity as compared to other approved quinolones."[9]

Symptoms of drug-induced liver disease are non-specific and may mimic many other illnesses. They include rash, loss of appetite, tiredness, pain on the right side just below the rib cage (where the liver is situated), dark urine or a yellowing of the skin or whites of the eyes (jaundice). The symptoms of liver toxicity may also include fever.

Trovafloxacin and alatrofloxacin (the intravenous form of the drug) are among the 39 drugs approved in 1997 when the FDA was under tremendous pressure, exerted by Congress, at the behest of the drug industry, to approve new drugs. This notorious class of '97 includes the diabetes drug troglitazone (REZULIN) that was withdrawn from the market in the United Kingdom because of liver toxicity, mibefradil (POSICOR) a heart drug banned worldwide because of fatal drug interactions, the painkiller bromfenac (DURACT) also withdrawn because of liver toxicity, and the dangerous diet drug sibutramine (MERIDIA) that was approved over the objections of the FDA's own Medical Officer and outside advisory committee of experts.

In conclusion, TROVAN is another example of a drug with no unique benefits and unquestionably unique, life-threatening risks. It should never have been approved. Now, with more of the liver damage predicted by the pre-marketing animal and human studies occurring in more than 100 reported cases (the actual number is likely well over 1,000 by now) including five deaths and three liver transplants, the drug must be immediately taken off the market. We look forward to a prompt response to this petition.

Sincerely,

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9 FDA Medical Officer's Safety Update (April 1998 to June 1998); pp. 5-6.