DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Keith E. Sharkin, Esq.
Nims, Howes, Collison, Hansen & Lackert
605 Third Avenue
Suite 3500
New York, New York 10158

Re: Docket No. 99P-1659/CP1

Dear Mr. Sharkin:

This responds to your citizen petition (Petition) dated May 26, 1999, on behalf of Novartis Pharmaceutical Corporation (Novartis) asking FDA to withdraw approval of Urso unless the name of the product is changed. You also request that the Agency require any future ursodiol product to use a name that does not incorporate or suggest the term "urso" (Petition at 2). For the reasons set out below, the Petition is denied.

Urso is the brand name of an ursodeoxycholic acid (ursodiol) product approved for the treatment of biliary cirrhosis and marketed by Axcan Pharma U.S., Inc. It is available in 250 milligram (mg) tablets. The recommended dosage for Urso is 13-15 mg/kg/day, administered in four divided doses with food. Novartis has an approved application for an ursodiol product named Actigall that is used for the treatment of gallbladder stones. It is 'available in 300 mg. capsules. The recommended dosage for Actigall is 8-10 mg/kg/day, in two or three divided doses.

Novartis asserts that there is a potential for medication errors from substituting Urso for Actigall and that this potential poses an imminent hazard to the public health (Petition at 1). The evidence Novartis offers is a survey it commissioned of 250 gastroenterologists, 250 pharmacists, and 60 surgeons in 10 metropohtan areas of the United States. According to Novartis, the survey shows that the short name "urso" is used to refer to ursodiol products and that Actigall is often called "urso" (Petition at 1, 3). Novartis concludes that "there is strong evidence that confusion, between URSO ursodiol products and other ursodiol products will be created as a result of the common usage of the sort name 'urso' and that such confusion is likely to lead to medication errors" (Petition at 4).

Novartis also presents affidavits from two physicians concerning the harm that would result if Urso were substituted for Actigall. Dr. Vivienne Matalon, an internist who treats obesity, states that substitution could lead to major problems for patients because they would receive a subtherapeutic dose. Dr. Thomas Garvey, a gastroenterologist, states that such substitution would result in underdosing by about 17 percent. Dr. Garvey assumes that the relationship between the risk of accumulation of gallstones and the total daily dose of Actigall is approximately linearly related to the logarithm of the daily dose and then extrapolates from clinical studies described in the labeling for Actigall (Petition at 4). He suggests that 17 percent underdosing would result in a 10 percent greater risk of gallstone accumulation in patients on very low calorie weight loss diets and a 24.4 percent increase in the risk of gallstone accumulation in patients experiencing rapid weight loss as a result of gastric bypass surgery.

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The survey Novartis commissioned is not persuasive. Methodologically, the survey has serious limitations. The information presented does not describe the sampling frames and does not explain the method by which the survey sample was selected. Thus, the Agency cannot evaluate the adequacy of the sample size. The survey does not appear to be a random sample. The very low response rate, 16 percent for gastroenterologists, 12 percent for surgeons, and 15 percent for pharmacists, undermines-the generalizability of the results. The design of the questionnaire was very poor because it relied on participants to complete open-ended questions regarding percentages, even though respondents were unlikely to have accurate percentage information. Furthermore, participants were not asked whether they knew of any actual medication errors.

In any event, the Agency does not believe that substitution of one ursodiol product for the other would present a serious safety risk. The notion that substitution of Urso for Actigall would increase the risk of gallstone formation is speculative, especially because it is not reasonable to assume that the substitution would go undetected for an indefinite period. Dr. Garvey's quantification of this theoretical risk is also speculative. The package inserts of both products state that there have been no reported cases of overdosing and that the most serious consequence of severe overdosing is likely to be diarrhea.

You also cite a memorandum from Axcan Director of Management Stephen M. Casey that was sent to members of an: on-line internet support group for patients with primary biliary cirrhosis (PBC). Mr. Casey states that "[m]any PBC patients have been treated with ACTIGALL and they have been improperly started at 10-12 mg/kg. This error commonly occurs because the dosing for ACTIGALL is based on its only approved use, the dissolution of gallstones" (Petition Exhibit C at 1.) What Mr. Casey is saying is that doctors prescribe Actigall for the unapproved use of PBC but use the dosing for the approved use. This does not support the Petition requests because it has nothing to do with the use of the name "Urso."

You offer no solid evidence to support the notion that Urso is likely to be substituted for Actigall. In fact, there is no evidence that medication errors have occurred. The Agency searched its Adverse Event Reporting System and its Drug Quality Reporting System for reports of confusion between Actigall and Urso and found none. The United States Pharmacopeia's database contained no reports of confusion between Actigall and Urso.

Moreover, Urso is a tablet and Actigall is a capsule, Urso is dosed four times a day, and Actigall is dosed two or three times a day. The Agency believes that these differences reduce the likelihood that one product would be substituted for the other.

You cite section 505(e) of the Federal Food, Drug, and Cosmetic Act as authority for your request to withdraw approval of Urso. Section 505(e)(l) provides for the withdrawal of an application for a drug when "clinical or other experience, tests, or other scientific data show that

such drug is unsafe for use under the conditions of use upon the basis of which the application was approved." FDA does not find that Urso is unsafe for use and therefore will not initiate proceedings to withdraw the approval of Urso.

You suggest that Urso poses an imminent hazard to the public health (Petition at 1). Section 505(e) of the Act states that "if the Secretary . . . rinds that there is an imminent hazard to the public health he may suspend the approval of such [new drug] application immediately" (2 1 USC 355(e)). The criteria for determining whether an imminent hazard exists are laid out in *Forsham v. Califano, 442* F. Supp. 203, 208-210 (D.D.C. 1977) as follows:

1. The severity of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drng from the general market.

2. The likelihood that the drug will cause such harm to Users while the administrative process is being completed.

3. The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the market taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.

4. The likelihood that after the customary administrative process is completed, the drug will be withdrawn from the general marketing.

5. The availability of other approaches to protect the public health.

As explained above, you have not established that withdrawal of Urso under the customary procedures is justified. The criteria for suspension of approval are much more stringent under the imminent hazard provision. *A fortiori*, therefore, you have not established that Urso presents an imminent hazard. Nor does the Agency find that there is a safety concern that needs to be addressed by requesting the manufacturer of Urso to voluntarily change the name of the product. Finally, if an application for another ursodiol 'product is submitted in the future, the Agency will consider the appropriateness of a name for that product at that time.

For the reasons discussed above, the Petition is denied.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research