



DRS/MH/IEA.57

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**DRS Information Exchange Service****ALERT No. 57****COMBINATION BARBITURATE PRODUCT (ATRIUM®) : HEPATOTOXICITY**

**France.** The Pharmacovigilance Committee has examined the results of a national enquiry concerning adverse reactions associated with the use of a fixed combination barbiturate product containing phenobarbital, febarbamate and difebarbamate (Atrium®: Riom Laboratories – CERM).

The 100 mg tablet formulation is indicated for the treatment of minor anxiety and the 300 mg tablets for the treatment of alcohol withdrawal symptoms. As for all anxiolytics available in France, the maximum duration of prescription is limited to 12 weeks. Liver damage is listed as an adverse reaction with the recommendation to stop treatment if increased transaminases or jaundice occurs.

Between 1 January 1986 to 30 June 1996, 148 cases of liver damage were reported to the national system or to the company. Onset after treatment varied considerably, and for 60% of cases the prescription duration exceeded the maximal duration of 12 weeks. An increase in transaminases of more than ten times the upper normal limit was recorded in half the cases. There were 40 cases of serious hepatitis (4 fatal), including 1 necessitating liver transplantation, 7 of cirrhosis or fibrosis at liver biopsy, 8 of hepatocellular failure and 20 of jaundice. Over the period 1990-1995 and for all dosages, the notification incidence was estimated to be 4.78 cases for 100,000 treatments, with 1.05 serious hepatic effects notified for 100,000 treatments.

Most of the other reported adverse reactions were cutaneous, including toxic bullous skin reactions, and osteo-muscular effects.

In agreement with the French Pharmacovigilance Committee, the French Advisory Board has considered that :

- Given the clinical data on efficacy provided by the company, and in view of the potential risk of liver damage, the benefit/risk ratio appears to be unfavourable for the use of Atrium® in the treatment of minor anxiety. Therefore the marketing authorization for the 100 mg dosage is to be withdrawn .
- Concerning the treatment of alcohol withdrawal syndrome, Atrium® 300 mg is specifically prescribed for the prevention of physical symptoms of withdrawal, such as convulsions, which can occur rapidly and require a short treatment duration. The major alternatives to Atrium® in the treatment of alcohol withdrawal symptoms – benzodiazepines and meprobamate – are associated with a risk of drug dependency and misuse. Furthermore, meprobamate is not effective against convulsions. Consequently, the therapeutic indication for Atrium® 300 mg should be limited to the treatment of alcohol withdrawal syndrome with a maximal treatment duration of 4 weeks, and the relevant sections of the SPC are to be modified.

A “Dear Doctor” letter has been sent on 26 March 1997 to all physicians and pharmacists concerning this decision which will be implemented after one month to avoid potential drug withdrawal syndrome and to give physicians enough time to decrease the dosage progressively before stopping the drug when this is relevant.

*Reference: Pharmacovigilance, Agence du Médicament, 4 April 1997.*