Information Exchange System

Alert No. 101

Leflunomide – severe and serious hepatic reactions

European Union. The Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) has been made aware of reports of serious liver injuries (including hepatitis, hepatic failure and very rare cases of acute hepatic necrosis), some with a fatal outcome, in patients with rheumatoid arthritis treated with leflunomide (Arava: Aventis). Arava was approved in the USA in 1998 and in the European Union in September 1999 and is currently marketed in all the EU member states and also in Norway.

Leflunomide is indicated for the treatment of adult patients with active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD). Leflunomide inhibits the enzyme dihydro-orotate dehydrogenase (DHODH) and exhibits antiproliferative activity.

A total of 296 cases with hepatic reactions have been reported in the context of extensive patient exposure (an estimated 104,000 patient years). Of these, 129 cases were considered as serious, including 2 cases of liver cirrhosis and 15 cases of liver failure, 9 with fatal outcome. Hepatic reactions appeared within 6 months of initiation of treatment. Confounding factors were present in many of these cases. Of the serious reports, 101 patients (78%) were concomitantly treated with hepatotoxic medications. In patients with elevated liver function tests, 58% were also being treated with methotrexate and/or NSAIDs. In addition, in 33 of these serious cases (27%) other risk factors were reported, including a history of alcohol abuse, liver function disturbance, acute heart failure, severe pulmonary disease or pancreatic carcinoma. Preliminary data on the prescribing profile of leflunomide suggest that monitoring recommendations might not have been fully adhered to. Prescribers are reminded that Arava® should only be prescribed by specialists experienced in the treatment of rheumatoid diseases.

In view of the seriousness of these reactions, the EMEA wishes to draw attention to the following:

Leflunomide is contraindicated in patients with impairment of liver function.

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within 6 months of initiation of treatment. Although confounding factors were present in many cases, a causal relationship with leflunomide cannot be excluded. It is considered essential that monitoring recommendations are strictly adhered to.

Concomitant treatment with methotrexate and/or other hepatotoxic medications is associated with an increased risk of serious hepatic reactions and is not advisable.

ALT (SGPT) must be checked before initiation and at monthly or more frequent intervals during the first six months of treatment and every 8 weeks thereafter.

For ALT (SGPT) elevations between 2 and 3 times the upper limit of normal, the dose may be reduced from 20 mg to 10 mg and monitoring should be performed weekly. If ALT (SGPT) elevations of more than 2 times the upper limit of normal persist or if ALT increases to more
than 3 times the upper limit of normal, leflunomide must be discontinued and wash-out procedures initiated.

If a severe undesirable effect of leflunomide occurs or if, for any other reason, the active metabolite needs to be cleared rapidly from the body (e.g. desired or unintended pregnancy, switching to another hepatotoxic DMARD such as methotrexate), the wash-out and monitoring procedures have to be followed (see SPC).

If a switch in treatment from leflunomide to another hepatotoxic DMARD is required, the wash-out and monitoring must be adhered to.

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure. The revised product information is available in the European Public Assessment Report of Arava published on the EMEA Website (http://www.eudra.org/humandocs/humans/epar/arava/arava.htm).

Note: Leflunomide has also been associated with reports of pancytopenia and serious skin reactions. The EMEA issued a public statement in this respect on 25 October 1999 (see also Alert No. 91 dated 11 November 1999, Internet address: http://www.who.int/medicines/drugalert/drugalert.html).

**Reference:**