The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

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EMEA PUBLIC STATEMENT ON LEFLUNOMIDE (ARAVA)
- SEVERE AND SERIOUS HEPATIC REACTIONS -

The European Medicines Evaluation Agency's (EMEA) scientific committee, the Committee for Proprietary Medicinal Products (CPMP) 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). Within the EU, Arava is currently marketed in all the EU member states and also in Norway[1].

Arava is indicated for the treatment of adult patients with active rheumatoid arthritis as a "disease-modifying antirheumatic drug"(DMARD). The active substance of Arava, leflunomide, inhibits the enzyme dihydroorotate 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 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 of liver function tests and wash-out procedures 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 to leflunomide cannot be excluded. It is considered essential that monitoring recommendations are strictly adhered to (as described below and in the SPC).**
- **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, 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.**

[1] On 2 September 1999 the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Arava, which contains leflunomide. The Marketing Authorisation Holder responsible for this medicinal product is Aventis Pharma Deutschland GmbH, Germany.

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- **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 washout and monitoring procedures (as summarised for ease of reference in the enclosed tables) and in the SPC have to be followed.**
- **If a switch in treatment from leflunomide to another hepatotoxic DMARD is required the washout and monitoring must be adhered to.**

As an urgent measure, the prescribing and patient information has been modified through a rapid procedure. The EMEA thought it necessary to provide this new information to the public. The revised product information is available in the European Public Assessment Report of Arava published on the EMEA Website.

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Summary of liver enzymes monitoring and washout procedures

Table 1: Liver enzyme monitoring of patients treated with leflunomide (Arava)

Routine monitoring of ALT (SGPT)	- **before the initiation** - **at monthly or more frequent intervals during the first 6 months of treatment and** - **every 8 weeks thereafter**
ALT (SGPT) between 2- and 3- ULN	- **a dose reduction from 20 mg to 10 mg may permit continued administration of leflunomide.** - **monitoring must be performed weekly.**
ALT (SGPT) > 3- ULN **or** **Persistent elevation of more than 2- ULN**	- **Leflunomide must be DISCONTINUED** - **A washout procedure should be introduced (Cholestyramine should be administered).**

Table 2: Washout procedure

Cholestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

Table 3: Circumstances where a washout procedure must be performed

- **switching from leflunomide to another DMARD (e.g. methotrexate).**
- **When serious undesirable effects occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions).**
- **In case of desired or unintended pregnancy (among other measures).**
- **or if for any other reason A771726 (the active metabolite of leflunomide) needs to be cleared rapidly from the body.**

PROVISIONAL CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS

Arava 10 mg film-coated tablets as relevant example

(Changes are highlighted)

INFORMATION TO PATIENTS (PACKAGE LEAFLET):

2. BEFORE YOU TAKE ARAVA

Take special care with Arava

Tell your doctor without any delay if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discoloration of the eyes or skin). Such symptoms may indicate the development of liver disorders which may need special action by your doctor (see also under point 4).

4. POSSIBLE SIDE-EFFECTS

Like all medicines, Arava may have side-effects.

Blood tests may show an increase in some liver test results~~, whereas severe disturbances in liver function are rare~~***, which in very rare cases may develop into serious conditions such as hepatitis and liver failure which may be fatal. Therefore, if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin), inform your doctor at once.***

INFORMATION TO PRESCRIBERS (SUMMARY OF PRODUCT CHARACTERISTICS):

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).

Recent ***or concurrent*** treatment with hepatotoxic or haematotoxic DMARDs ***(e.g. methotrexate)*** may result in ~~increased side effects~~***an increased risk of serious adverse reactions;*** therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without ~~a washout period~~ ***following the washout procedure (see section 4.4)*** may also increase the risk of serious adverse reactions even for a long time after the switching.

4.2 Posology and method of administration

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 (see also section 4.4).

A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter (see also section 4.4).

4.4 Special warnings and special precautions for use

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable.

~~For the management of the above-mentioned toxicities or when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide is indicated, a washout procedure should be performed as detailed below (see required monitoring and washout procedures).~~

For washout procedures ***and other recommended actions*** in case of desired ***or unintended*** pregnancy see section 4.6.

Liver reactions

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Comedication with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations are strictly adhered to.

~~AST (SGOT) and~~ ***ALT (SGPT) must be checked before*** ~~the start of leflunomide treatment and periodically therafter~~ ***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-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly. ~~For persisting~~ ***If*** ALT (SGPT) elevations of more than 2-***fold the upper limit of normal persist*** ~~to~~ ***or if ALT elevations of more than*** 3-fold the upper limit of normal ***are present***, leflunomide ~~should~~ ***must*** be discontinued ***and wash-out procedures initiated.*** ~~Cholestyramine can be administered to more rapidly lower A771726 levels.~~

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients with hypoproteinaemia ~~or impairment of liver function~~. Arava is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Switching to other treatments

As leflunomide has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without ~~a washout period~~ ***performing the washout procedure (see below)*** may raise the possibility of additive risks even for a long time after the switching (i.e. kinetic interaction, organ toxicity).

4.8 Undesirable effects

Gastrointestinal system, liver

Rare: ***hepatitis, jaundice/cholestasis and very rarely, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal***