Leflunomide medac- Physician Leaflet

Dear Doctor,

In addition to the Summary of Product Characteristics, this leaflet was developed by the marketing authorisation holder to inform you about all delicate issues potentially arising from Leflunomide medac therapy.

Counselling patients on important risks associated with Leflunomide medac therapy and appropriate precautions when using the medicine is required.

NOTE: Leflunomide medac should only be prescribed by rheumatologists who have fully familiarised themselves with the efficacy and safety profile of the active ingredient leflunomide.

Important information on hepatotoxicity and haematoxicity

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most cases of severe liver injury occur within 6 month of therapy. Cotreatment with other hepatotoxic medicinal products was frequently present.

- Leflunomide medac is contraindicated in patients with impairment of liver function.
- Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable. It is recommended that alcohol consumption be avoided during treatment with leflunomide.
- Leflunomide is contraindicated in patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis. In case of severe haematological reactions, including pancytopenia, leflunomide and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated.

Laboratory tests

- ALT (SGPT) and a complete blood cell count must be checked before initiation of leflunomide and every 2 weeks during the first 6 months of treatment and every 8 weeks thereafter.
- For confirmed ALT elevations between 2- and 3-fold ULN, **dose reduction** to 10 mg/day may allow continued administration of Leflunomide medac under weekly monitoring. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be **discontinued** and washout procedures initiated. It is

recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

Pregnancy contraindication

Pregnancy must be excluded before the start of the treatment with leflunomide. Leflunomide is contraindicated in pregnant women or women of childbearing potential who are not using a reliable contraception. Pregnancy must be avoided during leflunomide treatment or prior to the completion of the drug elimination procedure after leflunomide treatment.

Based on animal studies, Leflunomide medac may increase the risk of foetal death or teratogenic effects.

Females of childbearing potential

- Do not start Leflunomide medac until the following steps are completed:
    - Pregnancy is excluded
    - Confirm that reliable contraception is being used
    - Fully counsel patients on the potential for serious risk to the foetus
- The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapid lowering of the blood level of the active metabolite, by instituting the drug elimination procedure described below, at the first delay of menses may decrease the risk to the foetus from leflunomide.

Females on Leflunomide medac who wish to become pregnant

- For women receiving leflunomide treatment and who wish to become pregnant, one of the following procedures is recommended in order to ascertain that the foetus is not exposed to toxic concentrations of A771726, the active metabolite of leflunomide.
- WWaiting period: After a 2-year waiting period, the A771726 plasma concentration is measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l no teratogenic risk is to be expected.
- Washout procedure: Following either of the washout procedures (see below), verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

Information for males

Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.

To minimise any possible risk, men wishing to father a child should consider discontinuation of use of leflunomide and start a washout procedure (see below). Following the washout procedure the A771726 plasma concentration is then measured for the first time and again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, and after a waiting period of at least 3 months, the risk of foetal toxicity is very low.

Advisory service

For further information regarding the A771726 measurements, please call 01786 458086 or contact leflunomide@medac.eu.

Risk of infection

- Leflunomide medac is contraindicated for the use in immuno-compromised patients
- Leflunomide medac is contraindicated in patients having severe infections

Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections. Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia). Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and perform the washout procedure.

Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients taking leflunomide among other immunosuppressants. Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

Combination with other DMARDs:

Leflunomide may act synergistically or additively in combination with other hepatotoxic or haematotoxic DMARDs, for example methotrexate. Concomitant treatment with other DMARDs is not advisable.

Washout Procedures

After stopping treatment with leflunomide

- Colestyramine 8 g is administered 3 times daily for a period of 11 days
- Alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

The duration may be modified depending on clinical or laboratory variables. Both colestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Abbreviations

ALT = alanine-aminotransferase

(formerly glutamate-pyruvate-transaminase = **GPT**)

AST = aspartate-aminotransferase

(formerly glutamate-oxalacetate-transaminase = **GOT**)