LEFLUNOMIDE NORMON 10mg/20mg FILM-COATED TABLETS GSP

LEFLUNOMIDE

Safety Information for Health Care Professionals

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

As part of the European registration process for Leflunomide, within the framework of the risk management plan for this medicine, the marketing authorisation holder has developed a training programme, including this leaflet, for prescribers of Leflunomide.

The aim of this training material is to minimise several risks that have been identified in the context of the European risk management plan established for Leflunomide.

The most important risks you should know when prescribing Leflunomide are:

- Risk of hepatotoxicity (very rare (<1/10,000 patients) cases of severe liver damage, which can be fatal, are listed in the summary of product characteristics).
- Risk of haematotoxicity (cases of pancytopenia, leukopenia and eosinophilia, with rare frequency of occurrence (≥ 1/10,000 to < 1/1,000 patients) and cases of agranulocytosis with very rare frequency of occurrence are included in the summary of product characteristics).
- Risk of infections (rare occurrences of severe uncontrolled infections (sepsis), which can be life-threatening, are included in the summary of product characteristics).
- Risk of serious birth defects when administered during pregnancy.

To minimise these risks, it is recommended to: properly counsel patients, carry out careful monitoring and follow the recommendations regarding the drug washout procedure.

Full details on Leflunomide are given in the currently authorised SmPC for this medicine.

COUNSELLING OF PATIENTS

Before starting treatment with Leflunomide, ensure that patients are adequately informed about the significant risks associated with the treatment and the appropriate precautions they should take to minimise these risks. To this end, the Marketing Authorisation Holder has developed, in addition to this information sheet for the physician, a specific information sheet for the patient.

ROUTINE BLOOD MONITORING

Due to the risk of hepatotoxicity and haematotoxicity, which in rare cases can be severe or even fatal (see tables below), careful monitoring of liver parameters and blood counts before and during treatment with Leflunomide is essential.
Additional information on these adverse reactions can be found in the Summary of Product Characteristics.

Concomitant administration of Leflunomide and hepatotoxic or haematotoxic disease-modifying antirheumatic drugs (DMARDs), e.g. methotrexate, is not recommended.

Monitoring of liver enzymes

ANALYTICAL TESTS	FREQUENCY
As a minimum, the ALT concentration (SGPT) should be determined	Before the start of treatment and every 2 weeks for the first six months of treatment
	Thereafter, if they are stable, every eight weeks
Confirmed elevation of ALT concentration	**Dose adjustment / Discontinuation**
Between 2 and 3 times the ULN*	Dose reduction from 20 mg/day to 10 mg/day may allow continued administration of Leflunomide with weekly monitoring.
2 to 3 times ULN is maintained despite dose reduction - OR - >3 times the ULN	Discontinue Leflunomide Start a washout procedure (see section "Washout procedure") and monitor liver enzymes until they normalise.

*ULN: Upper limit of normality

Haematological monitoring

ANALYTICAL TESTS	FREQUENCY
Complete blood count, including white blood cell count and platelet count	Before the start of treatment and every 2 weeks for the first six months of treatment
	Thereafter, every eight weeks
Discontinuation	
Severe haematological reactions including pancytopenia	Discontinue Leflunomide and any concomitant myelosuppressive therapy Start a washout procedure (see section "Washout procedure")

INFECTIONS

The immunosuppressive properties of Leflunomide may make patients more susceptible to infections, including opportunistic infections.

In rare cases, serious infections such as progressive multifocal leukoencephalopathy (PML) or severe uncontrolled infections (e.g. sepsis) may occur.

Patients with a positive tuberculin reaction should be closely monitored because of the risk of tuberculosis. In case of severe, uncontrolled reactions, it may be necessary to discontinue leflunomide treatment and start a washout procedure (see section "Washout procedure").

Leflunomide is contraindicated in:

- Patients with severe immunodeficiency states, e.g., AIDS.
- Patients with severe infections

PREGNANCY

Women of childbearing age, women who wish to become pregnant and men who wish to become fathers should be informed about the risk of birth defects associated with taking Leflunomide and the need to use effective contraception. They should also be informed about the measures to be taken in case of pregnancy during or after treatment. This information should be provided before treatment begins, regularly throughout the duration of treatment, and after treatment has ended for up to 2 years.

Risk of birth defects

Based on data from animal studies, the active metabolite of Leflunomide is suspected to cause serious birth defects when administered during pregnancy. Leflunomide is therefore contraindicated during pregnancy.

Women

STATUS	RECOMMENDATIONS
Women of childbearing age	Effective contraception is required during treatment and for up to 2 years after discontinuation. Pregnancy must be excluded before starting of treatment with leflunomide.
Any delay in the menstrual cycle OR Any other reason why pregnancy is suspected	Take a pregnancy test immediately
	If pregnancy is confirmed: • Discontinue Leflunomide • Start a washout procedure (see below) • Carry out tests of plasma concentrations of A771726 (see below) • Inform the patient of the risks of pregnancy

Women who wish to become pregnant	• Inform the patient of the risks of pregnancy, as well as the 2-year waiting period required after discontinuation of treatment before they can become pregnant. If this waiting period with an effective contraceptive method is considered impractical, a preventive washout procedure is advised. • Start the washout procedure (see below) • Carry out tests of plasma concentrations of A771726 (see below)

o Washout procedure

Starting the washout procedure (see section "Washout procedure") avoids the 2-year waiting period before becoming pregnant. Both cholestyramine and powdered activated charcoal are capable of modifying the absorption of oestrogens and progestogens, so the use of alternative methods of contraception over oral contraceptives is recommended throughout the washout procedure.

If the washout procedure cannot be performed, the woman must undergo a 2-year waiting period after discontinuation of treatment before becoming pregnant. An effective method of contraception must be used during these two years. 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 expected.

o Tests that must be done at the end of the washout period

Two independent tests must be carried out, at least 14 days apart.

- If the results of the 2 tests are < 0,02 mg/l (0,02 µg/mL), no further test is necessary. A waiting period of one and a half months is required between the first result < 0.02 mg/l and fertilisation.
- If the results of one of the tests are > 0,02 mg/l (0,02 µg/mL), the washout procedure must be repeated with 2 independent tests 14 days apart.

A waiting period of one and a half months is required between the first observation of a plasma concentration below 0.02 mg/l and fertilisation.

Men

Due to the possibility of foetal toxicity produced by males taking Leflunomide, the use of an effective method of contraception should be ensured during treatment with Leflunomide.

For men who want to become fathers, the same washout procedure recommended for women should be considered.

A waiting period of three months is required between the first observation of a plasma concentration below 0.02 mg/l and fertilisation.

WASH-OUT PROCEDURE

Plasma concentrations of the active metabolite of leflunomide A771726 can be expected to remain above 0.02 mg/l for an extended period of time. Its concentration is expected to fall below this level around 2 years after discontinuing Leflunomide treatment.

To accelerate the elimination of A771726, when it is necessary to remove it rapidly from the body, it is recommended to perform the washout procedure described in the table below.

EVENTS LEADING TO A WASHOUT PROCEDURE	PROTOCOL OF THE WASHOUT PROCEDURE
Severe haematological and hepatic reactions Serious uncontrolled infections (e.g. sepsis) Pregnancy – planned or not Other events that could lead to the washout procedure: • Skin and/or mucosal reactions (e.g. ulcerative stomatitis), with suspected serious reactions, such as Stevens - Johnson syndrome or toxic epidermal necrolysis • After discontinuation of Leflunomide treatment and switch to other DMARDs* (e.g. methotrexate) which may increase the possibility of cumulative risk • For any other reason requiring rapid elimination of the active metabolite of Leflunomide from the body . *DMARDs: Disease-modifying antirheumatic drugs	After discontinuing Leflunomide: • Cholestyramine 8 g 3 times a day (24 g per day) for 11 days Oral administration of cholestyramine to 3 healthy volunteers, at a dose of 8 g 3 times daily over 24 hours, reduced plasma concentrations of the active metabolite A771726 by approximately 40% over 24 hours and by 49 - 65% over 48 hours. OR • 50 g powdered activated charcoal 4 times a day (200 g per day) for 11 days Administration of activated charcoal (powder for suspension) orally or via nasogastric tube (50 g every 6 hours over 24 hours) has been shown to reduce plasma concentrations of the active metabolite A771726 by 37% over 24 hours and 48% over 48 hours. The duration of the washout protocol can be modified according to clinical or analytical variables.

Further copies of this material or patient material can be requested from any of the Leflunomide Licensees, or printed from the website of the Malta Medicines Authority: www.medicinesauthority.gov.mt/rmm

Kindly remember the importance of reporting suspected adverse reactions. In the event of a suspected adverse event, please report it to:

Mint Health Ltd., 3/4 Cantrija Complex, Triq it-Targa, Il-Maghtab, Naxxar NXR6613 Malta
Tel: +356 2093 9800
Email: pharmacovigilancemt@mint.com.mt.

Alternatively, suspected adverse reactions should be reported to:

ADR Reporting Sir Temi Zammit Buildings, Malta Life Sciences Park,San Gwann SGN 3000, Malta
Email: postlicensing.medicinesauthority@gov.mt
Website: www.medicinesauthority.gov.mt/adrportal

Date of approval of document by Malta Medicines Authority: 22/04/2024