ARAVA
(leflunomide)

Specific Safety Information

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

As part of the European registration of leflunomide, in the context of the risk management plan of this product, the Marketing Authorization Holder has developed an educational program, including this physician leaflet for physicians who prescribed or will prescribe leflunomide.

This educational material is intended to minimize several risks identified in the frame of the European risk management plan established for leflunomide.

The most important risks you should be aware of when prescribing leflunomide include:

- Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
- Risk of hematotoxicity, including rare cases of pancytopenia, leukopenia, eosinophilia and very rare cases of agranulocytosis
- Risks of infections including rare cases of severe uncontrolled infections (sepsis), which may be fatal
- Risk of serious birth defects when administered during pregnancy

Counselling of patients, careful monitoring and following recommendations regarding the wash-out procedure are required to minimize these risks.

Complete prescribing information is provided in the approved Summary of Product Characteristics for leflunomide.

The summary of product characteristics (SmPC) are available on the Medicines information online website **www.medicines.ie**

COUNSELLING OF PATIENTS

Before starting the treatment with leflunomide, please ensure that patients have been counselled on all important risks associated with leflunomide therapy and appropriate precautions to minimize these risks. To this aim, a Specific Patient Leaflet has been developed by the Marketing Authorisation Holder in addition to the present safety information sheet.

ROUTINE BLOOD MONITORING

Due to the risk of hepato- and hematoxicity, which in rare cases can be severe or even fatal (see Tables below), a careful monitoring of hepatic parameters and blood cell count before and during treatment with leflunomide is essential.
More information about the occurrence of these adverse effects is available in the Summary of Product Characteristics.

Concomitant administration of leflunomide and hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) is not advisable, see section 4.4 of the SmPC.

Switching to other treatments
As leflunomide has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without 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).
Similarly, recent treatment with hepatotoxic or hematotoxic medicinal products (e.g. methotrexate) may result in increased side effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

Liver enzyme monitoring

LABORATORY TESTS	FREQUENCY
At minimum ALT (SGPT) must be performed	Before initiating treatment and every 2 weeks during the first 6 months of treatment
	Then, if stable, every 8 weeks thereafter
Confirmed ALT Elevations	**Dose Adjustment/Discontinuation**
Between 2- and 3-fold ULN*	Dose reduction from 20 mg/day to 10 mg/day may allow for continued administration of leflunomide under weekly monitoring
2- to 3-fold ULN persists despite dose reduction - Or- >3-fold ULN is present	Discontinue leflunomide Initiate a wash-out procedure (see section 'Wash-out procedure') and monitor the liver enzymes until normalization

* ULN: Upper Limit of Normal

Hematologic monitoring

LABORATORY TESTS	FREQUENCY
A complete blood cell count, including differential white blood cell count and platelets	Before initiating treatment and every 2 weeks during the first 6 months of treatment
	Then, every 8 weeks thereafter
Discontinuation	
Severe hematologic reactions, including pancytopenia	Discontinue leflunomide and any concomitant myelosuppressive treatment Initiate a wash-out procedure (see section 'Wash-out procedure')

INFECTIONS

Leflunomide immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections, and may rarely cause severe uncontrolled infections (e.g sepsis) as well as infections severe in nature, such as Progressive Multifocal Leukoencephalopathy (PML).

Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis as per local recommendation

In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a wash-out procedure (see section 'Wash-out procedure').

Leflunomide is contraindicated in:

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

PREGNANCY

Please inform the women of childbearing potential, women who plan to become pregnant and men planning to father a child, about the risk of birth defects with leflunomide and the necessity to use reliable contraception. Please also discuss the measures to follow in case of unplanned pregnancy during treatment and after treatment's discontinuation. This information should be given before treatment, regularly during treatment and after treatment.

Risk on birth defects

Based on animal studies, the active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Therefore leflunomide is contraindicated in pregnancy.

Women

STATUS	RECOMMENDATIONS
Women of childbearing potential	Effective contraception required during treatment and up to 2-years after treatment discontinuation
Any delay in onset of menses Or Any other reason to suspect pregnancy	Pregnancy testing immediately
	If confirmed pregnancy: ▪ Discontinue leflunomide ▪ Initiate a wash-out procedure (see below) ▪ Perform A771726 plasma level analysis (see below) ▪ Discuss the risks to the pregnancy with the patient
Women wishing to become pregnant	▪ Discuss the risks to the pregnancy with the patient, and inform her of the required waiting period of 2 years after treatment discontinuation before she may become pregnant. If this waiting period under reliable contraception is considered unpractical, prophylactic institution of a wash-out procedure may be advisable. ▪ Initiate the wash-out procedure (see below) ▪ Perform A771726 plasma level analysis (see below)

○ Wash-out procedure

Start the wash-out procedure (see section 'Wash-out procedure') which allows avoiding the 2-year waiting period. Both colestyramine and activated powdered charcoal are able to modify the absorption of oestrogens and progestogens, therefore use of alternative contraceptive methods other than oral contraceptives is recommended during the entire wash-out period.

If the wash-out procedure can not be performed, a 2-year waiting period under reliable contraception is required after treatment discontinuation before becoming pregnant.

○ Testing at the end of the wash-out period

Two separate tests at an interval of at least 14 days must be performed.

- If the 2 test results are < 0.02 mg/L (0.02 µg/mL), no further procedures are necessary. A waiting period of one-and-a-half months between the first result < 0.02 mg/L and fertilization is required.
- If results of either test are > 0.02 mg/L (0.02 µg/mL), the wash-out procedure must be performed again, with 2 separate tests at 14 days of interval.

Between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation, a waiting period of one-and-a-half months is required.

Men

As there is a possible male-mediated foetal toxicity, reliable contraception during treatment with leflunomide should be guaranteed.

For men planning to father a child, the same wash-out procedure as recommended for women should be considered.

Between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation, a waiting period of 3 months is required.

Ad hoc advisory service

An ad hoc advisory service is available for providing information on leflunomide plasma level testing for patients treated with leflunomide. Please contact Sanofi Ireland Medical Information on **01 4035600** or **IEmedinfo@sanofi.com**.

WASH-OUT PROCEDURE

Plasma levels of the active metabolite of leflunomide, A771726 can be expected to be above 0.02 mg/L for a prolonged period. The concentration may be expected to decrease below 0.02 mg/L about 2 years after stopping the treatment with leflunomide.
The wash-out procedure described in the table below is recommended to accelerate A771726 elimination, when it needs to be cleared rapidly from the body.

EVENTS WHERE WASH-OUT PROCEDURE IS RECOMMENDED	WASH-OUT PROCEDURE PROTOCOL
Severe hematologic and hepatic reactions Severe uncontrolled infections (e.g sepsis) Pregnancy – planned or not Other events leading to a wash-out procedure: • Skin and/or mucosal reactions (e.g. ulcerative stomatitis), with suspicion of severe reactions, such as Stevens Johnson syndrome or toxic epidermal necrolysis • After leflunomide discontinuation and a switch to another *DMARD (e.g. methotrexate) which may increase the possibility of additive risk • For any other reason requiring quick elimination of the active metabolite of leflunomide from the body	After stopping treatment with leflunomide: • Colestyramine 8 g 3 times daily (24 g per day) for 11 days *Colestyramine given orally at a dose of 8 g 3 times a day for 24 hours to 3 healthy volunteers decreased plasma levels of the active metabolite A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.* Or • 50 g of activated powdered charcoal 4 times daily (200 g per day) for 11 days *Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite A771726 by 37% in 24 hours and by 48% in 48 hours.* The duration of the wash-out protocol may be modified depending on clinical or laboratory variables.

Communication

Patient safety is the highest priority for Sanofi and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe leflunomide appropriately. Please review carefully the enclosed and contact Sanofi Ireland Medical Information on **01 4035600** or **IEmedinfo@sanofi.com** if you have any additional questions or if you require additional copies of the educational material.

Call for Reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions by contacting HPRA Pharmacovigilance, website: **www.hpra.ie**.

Adverse reactions should also be reported to Sanofi: Tel: **01 403 5600**, e-mail: **IEPharmacovigilance@sanofi.com**