

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 risk 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 serious birth defects when administered during pregnancy (teratogenicity)
- Risk of male mediated foetal toxicity

Counselling of patients 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 and www.hpra.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.

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: <ul style="list-style-type: none">Discontinue leflunomideInitiate 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	<ul style="list-style-type: none">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.

WASHOUT PROCEDURE PROTOCOL

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 events via HPRA Pharmacovigilance. Website: **www.hpra.ie**.

Adverse events should also be reported to the Sanofi drug safety department: Tel: **01 403 5600**, e-mail: **IEPharmacovigilance@sanofi.com**

This physician leaflet has been approved by the Health Products Regulatory Authority (HPRA).

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