Specific Safety Information

Arava® (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 Arava®, in scope 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 Arava®.

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

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

- Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
- Risk of hematotoxicity, including rare cases of pancytopenia, leucopenia, 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 minimise these risks.

Complete prescribing information is provided in the currently approved Summary of Product Characteristics for Arava® (see attached).

COUNSELLING OF PATIENTS

Before starting the treatment with Arava®, please ensure that patients have been counselled on important risks associated with Arava® 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 Arava® is essential.
More information about the occurrence of these adverse effects is available in the Summary of Product Characteristic.

Concomitant administration of Arava® and hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) is not advisable.

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 Arava® under weekly monitoring
2- to 3-fold ULN persists despite dose reduction - Or- >3-fold ULN is present	Discontinue Arava® 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 Arava® and any concomitant myelosuppressive treatment Initiate a wash-out procedure (see section 'Wash-out procedure')

INFECTIONS

Arava® 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).

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis.

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').

Arava® 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 wish to become pregnant and men wishing to father a child, about the risk of birth defects with Arava® and the necessity to use reliable contraception. Please also discuss the measures to follow in case of inadvertent 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 Arava®, A771726 is suspected to cause serious birth defects when administered during pregnancy. Therefore Arava® 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 Arava® ▪ 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)

o 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 progestrogens, 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.

o 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 Arava® should be guaranteed.

For men wishing 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 Arava®. Please contact Sanofi-Aventis Malta Ltd to obtain further information concerning this service on tel: 21493022/3

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 Arava®.
The wash-out procedure described in the table below is recommended to accelerate A771726 elimination, when its needs to be cleared rapidly from the body.

EVENTS LEADING TO A WASH-OUT PROCEDURE	WASH-OUT PROCEDURE PROTOCOL
Severe hematologic and hepatic reactions	After stopping treatment with Arava®: • 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.
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 Arava® 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 Arava® from the body	

Call for reporting:
Healthcare professionals should report any adverse events suspected to be associated with the use of ARAVA to Sanofi Malta Ltd., 3rd Floor, Avantech Building, St. Julian's Road, San Gwann SGN 2805. Tel: 21493022, fax 21493024

Alternatively any suspected ADRs and medication errors can be reported to the Medicines Authority. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt