[August 10th 2011]

Information Letter Regarding Important Safety Aspects to Optimize Arava® Therapy

Dear Healthcare Professional:

Healthcare professionals should familiarize themselves with the measures that should be taken to minimize the risks of hepatic reactions, teratogenicity, and the contraindications when prescribing or using Arava® (Leflunomide).

You should be aware of the following important risks when prescribing Arava®:

- Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
- Risk of serious birth defects when administered during pregnancy

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

Counseling of patients:

Before starting the treatment with Arava®, please ensure that patients have been counseled on important risks associated with Arava® therapy.

Routine blood monitoring:

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

Pregnancy :

Pregnancy must be excluded, where appropriate, before the start of the treatment with leflunomide. Leflunomide is contraindicated in pregnant women; and women of childbearing potential who are not using a reliable method of contraception. Pregnancy must be avoided during leflunomide treatment and prior to the completion of the drug elimination procedure (see "Wash-out procedure") after leflunomide treatment. Passive elimination of leflunomide resulting in concentrations of the active metabolite which are considered to present negligible risk to the unborn child may take up to 2 years. 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 A ny 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, prophylcatic 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 allow avoiding the 2 year waiting period. Both colestyramine and activated powdered charcoal are able to modify the absorption of oestragens and progestrogens, therefore use of alternative contraceptive methods other than oral contraceptive 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 A771726 plasma level analysis at an interval of at least 14 days must be performed.

- If the 2 tests 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/L), 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 fertilization, a waiting period of 6 weeks 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 fertilization, a waiting period of 3 months is required.

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 it needs to be cleared rapidly from the body.

EVENTS WHERE WASH-OUT PROCEDURE IS RECOMMENDED	WASH-OUT PROCEDURE PROTOCOL
Severe hematologic an hepatic reactions Sever uncontrolled infection (e.g.sepsis) Pregnancy – planned or not Other event leading to a wash-out procedure: • Skin and/or mucosal reaction (e.g. ulcerative stomatitis), with suspicion of severe reactions, such as Steven 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	After stopping treatment with Arava®: • Cholestyramine 8 g 3 times daily (24 g per day) for 11 days Cholestyraminegivenorally at a dose of 8 g 3 times a day for 24 hours to 3 healthy volunteers decrease 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 Administrationof 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 in clinical laboratory variables.

The Summary of Product Characteristics and the Package Insert Leaflet approved by the SFDA on October 2010 includes the above information. Please find them enclosed.

Call for Reporting

Patient safety is the highest priority for Sanofi Aventis and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe Arava® appropriately. Please review carefully the enclosed and contact sanofi-aventis if you have any additional questions.

Any suspected adverse events experienced by your patients should be reported to the national Pharmacovigilance center in Saudi Arabia.

Saudi Food and Drug Authority
National Pharmacovigilance Center
Tel: +966 1 2759222
Exts: 2317, 2356, 2353, 2354, 2334 & 2340
Fax: +966 1 2057662
E-Mail: npc.drug@sfda.gov.sa

In addition, suspected adverse reactions related to sanofi-aventis products may be reported to sanofi aventis pharmacovigilance department:

Email: KSA_Pharmacovigilance@sanofi-aventis.com
Contact person: **Dr Mohamed El-Tawwab**
Tel: +966 1 4633190 Ext 1147
Mobile: +966 564095175 / +966 564095014

For further information:

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Ext : 1152 & 1104
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We remain at your disposal for any further information you may need.

Yours sincerely,

Sharif Galal, MD
Director Medical Affairs

Sanofi Aventis
Saudi Arabia

Attachements:
SmPC approved in Saudi Arabia in October 2010
PIL approved in Saudi Arabia in October 2010