11-Aug-2021

Arava (LEFLUNOMIDE): Specific Safety Information

Leflunomide Winthrop® 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 scope of the risk management plan of this product, the Marketing Authorization Holder has developed an educational program, including this physician let 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, 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 minimize these risks.

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

COUNSELLING OF PATIENTS

Before starting the treatment with Leflunomide, please ensure that patients have been counselled on 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 Characteristic.

Concomitant administration of Leflunomide 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 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).

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').

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 wish to become pregnant and men wishing 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 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 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 progestrogens, therefore use of alternative contraceptive methods other than oral contraceptives is recommended during the entire wash-out period.

If the wash-out procedure cannot 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 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 Leflunomide. Please contact sanofi-aventis company to obtain further information concerning this service

For further medical information, please contact Sanofi at:
E-mail: ksa.medicalinformation@sanofi.com
Web: https://www.sanofi.com.sa/ - Landline : +966 12 669 3318

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 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 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.
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	

Any suspected adverse events or adverse drug reactions should be reported to:

The National Pharmacovigilance Centre (NPC):
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

SANNOFI PV 24/7 contact number: +966 544284797

Email: KSA_pharmacovigilance@sanofi.com
Address: Sanofi, KSA | Tahlia St., Nojoud Center, Gate B, 2nd Floor.
P.O.Box 9874, Jeddah 21423, KSA

LEFLUNOMIDE WINTHROP® SUMMARY OF PRODUCT CHARACTERISTICS

TRADE NAME OF THE MEDICINAL PRODUCT AND PRESENTATION:
Arava® is available in film coated tablets containing 10 mg of leflunomide \ 20 mg of leflunomide.
THERAPEUTIC INDICATIONS: • Active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).
• Active psoriatic arthritis. Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.
POSOLOGY AND METHOD OF ADMINISTRATION: The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis. Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:
• before initiation of leflunomide. • every two weeks during the first six months of treatment, and • every 8 weeks thereafter.
Posology: • In rheumatoid arthritis: leflunomide therapy is usually started with a loading dose of 100 mg once daily for 3 days. Omission of the loading dose may decrease the risk of adverse events. The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease. • In psoriatic arthritis: leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days.
The recommended maintenance dose is leflunomide 20 mg once daily. The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. There is no dose adjustment recommended in patients with mild renal insufficiency. No dose adjustment is required in patients above 65 years of age.
Paediatric population: Arava is not recommended for use in patients below 18 years since efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established.
Method of administration: Arava tablets are for oral use. The tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.
CONTRAINDICATIONS: Hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the active substance, to the principal active metabolite teriflunomide or to any of the excipients.
• Patients with impairment of liver function.
• Patients with severe immunodeficiency states, e.g. AIDS.
• Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
• Patients with serious infections.
• Patients with moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group.
• Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.
• Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/L. Pregnancy must be excluded before start of treatment with leflunomide.
• Breast-feeding women.
SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE: Coadministration of hepatotoxic/hematotoxic DMARD is not advisable. Rare cases of severe liver injury, including cases with fatal outcomehave been reported. Check SGPT before treatment initiation, every 2 weeks during first six months and every 8 weeks thereafter. Increased risk of haematological disorders in patients with pre-existing anemia, leucopenia, and/or thrombocytopenia, impaired bone marrow function/at risk of bone marrow suppression. In case of severe haemotological reactions, including pancytopenia, discontinue treatment and initiate washout procedure. The use of leflunomide with antimalarials (e.g. chloroquine, hydroxychloroquine), intramuscular or oral gold, Dpenicillamine, azathioprine and other immunosuppressive including Tumour Necrosis Factor alpha-inhibitors has not been adequately studied. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive toxicity (e.g. hepato- or haematotoxicity), combination with another DMARD (e.g. methotrexate is not advisable. Recent treatment with hepatotoxic/haemototoxic products may result in increased side effects. Ulcerative stomatitis. More susceptible to infections, including opportunistic infections. Respiratory reactions: Interstitial lung disease. Peripheral neuropathy. Check blood pressure before starting the treatment. Possible male-mediated foetal toxicity. Lapp lactase deficiency or glucose-galactose malabsorption. Pustular psoriasis and worsening of psoriasis, Colitis, have been reported after the use of leflunomide. Before starting treatment, active and inactive tuberculosis should be evaluated. Interference with determination of ionized calcium levels.
INTERACTIONS: Increase side effects in coadministration with hepato- /haematotoxic drug, close monitoring of liver and haematological parameters is recommended after switching. Colestyramine or activated powdered charcoal lead to a rapid and significant decrease active metabolite plasma concentration. Vaccination with live attenuated vaccines is not recommended. Caution is advised when leflunomide is given together with warfarin and other coumarine anticoagulants, NSAIDS/Corticosteroids, CYP450 inhibitors and inducers, oral contraceptives, repaglinide, caffeine, OAT3 substrates, BCRP and /or OATP1B1/B3 substrates. Co-administration of teriflunomide with leflunomide is not recommended
PREGNANCY AND LACTATION: Arava is contraindicated in pregnancy, if patient wish to pregnant follow waiting period or washout procedure. Animal studies indicates leflunomide and its metabolites pass into breast milk.
UNDESIRABLE EFFECTS: The most frequently adverse effects reported commonly (>1/100 to <1/10) are mild increase in blood pressure, leucopenia, paraesthesia, headache, dizziness, colitis, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain, increased hair loss, eczema, rash (including maculo-papular rash), pruritus, dry skin, tenosynovitis, CPK increased, anorexia, weight loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases (especially ALT), less often gamma-GT, alkaline phosphatise, bilirubin)).
OVERDOSAGE: No adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: abdominal pain, nausea diarrhea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.
PHARMACOLOGICAL PROPERTIES: Selective immunosuppressive agents.
WARNING: EMBRYO-FETAL TOXICITY AND HEPATOTOXICITY
Embryo-Fetal Toxicity
ARAVA is contraindicated for use in pregnant women because of the potential for fetal harm. Teratogenicity and embryotoxicity occurred in animals administered leflunomide at doses in the human therapeutic range. Exclude pregnancy before the start of treatment with ARAVA in females of reproductive potential. Advise females of reproductive potential to use effective contraception during ARAVA treatment and during an accelerated drug elimination procedure after ARAVA treatment. Stop ARAVA and use accelerated drug elimination procedure if the patient becomes pregnant.
Hepatotoxicity
Severe liver injury, including fatal liver failure, has been reported in patients treated with ARAVA. ARAVA is contraindicated in patients with impairment of liver function. Concomitant use of ARAVA with other potentially hepatotoxic drugs may increase the risk of liver injury. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT)>2xULN before initiating treatment, are at increased risk and should not be treated with ARAVA. Monitor ALT levels at least monthly for six months after starting ARAVA, and thereafter every 6-8 weeks. If leflunomide-induced liver injury is suspected, stop ARAVA treatment, start an accelerated drug elimination procedure, and monitor liver tests weekly until normalized.

This abbreviated product information has been revised on April 2021

LEFLUNOMIDE WINTHROP®

Specific Patient Information

This information sheet has been developed in accordance with the current Leflunomide (leflunomide) Package leaflet and should be read in addition to this Package leaflet inserted in the medication packaging.

What should you know if you are a woman of childbearing potential, a woman with a wish to become pregnant or a man wishing to be a father?

If you are a woman of childbearing potential or a woman with a wish to become pregnant

Leflunomide may increase the risk of serious birth defects

You may be at increased risk of having a baby with a birth defect if:

- You are pregnant when you start taking Leflunomide, or
- You become pregnant while you are taking Leflunomide, or
- You do not wait to become pregnant until you have stopped taking Leflunomide and followed the drug wash-out procedure described below, or
- You become pregnant within 2-years after you stopped Leflunomide

Precautions of use for Leflunomide

If you are a woman of childbearing potential, you and your partner should take every precaution to avoid becoming pregnant, such as both partners using reliable birth control as recommended by your doctor when:

- You are currently taking Leflunomide, or
- You have discontinued Leflunomide and are going through the drug wash-out procedure, or
- You have discontinued Leflunomide less than 2-years ago

It is VERY IMPORTANT that you contact your doctor IMMEDIATELY if your menstrual period is at all late or if for any other reason you believe you may be pregnant.

Leflunomide wash-out procedure

After discontinuing Leflunomide, your doctor will order you a drug wash-out procedure.

The aim of this procedure is to remove the drug rapidly and sufficiently from your body. The wash-out procedure consists of a full 11-day course of certain drugs which speed up the removal of Leflunomide from your body. This course is followed by 2 separate laboratory blood tests at least 14 days apart to assure a very low drug level in your body. If your Leflunomide levels are still too high, a repeated drug wash-out procedure may be necessary.

When it is confirmed that Leflunomide has been sufficiently removed from your body by the 2 separate laboratory blood tests, you should then wait for at least another month before you become pregnant.

If you do not follow the drug wash-out procedure, it could take up to 2 years to reach this very low drug level in your blood.

If you are a man wishing to be a father

As it can not be excluded that Leflunomide passes into semen, reliable contraception during treatment with Leflunomide should be guaranteed.

When you want to father a child, you should discuss with your doctor who could advise you stop Leflunomide and then undergo the drug wash-out procedure (as described above).

When it is confirmed that Leflunomide has been sufficiently removed from your body, men should then wait for at least 3 months before fertilisation.

For further information, please contact your doctor.

Any suspected adverse events or adverse drug reactions should be reported to:

The National Pharmacovigilance Centre (NPC):
SFDA call center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

SANNOFI PV 24/7 contact number: +966 544284797
Email: KSA_pharmacovigilance@sanofi.com
Address: Sanofi, KSA | Tahlia St., Nojoud Center, Gate B, 2nd Floor.
P.O.Box 9874, Jeddah 21423, KSA