Arava®20
Arava®100

[sanofi logo]

Active ingredient: Leflunomide

This package insert is continually updated: please read carefully before using a new pack!

Composition
Each film-coated tablet Arava **20** contains, as active ingredient, 20 mg leflunomide
Each film-coated tablet Arava **100** contains, as active ingredient, 100 mg leflunomide
Excipients: Maize starch, Povidone, crospovidone, talc, silica colloidal anhydrous, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, macrogol 8000 and – Arava **20** only – yellow ferric oxide.

Properties
Pharmaco-therapeutic class: Antirheumatic, immunosuppressive agents (L: antineoplastic and immunomodulating agents).
ARAVA belongs to a group of substances (isoxazole derivatives), which is a class of antirheumatic medicines. In active rheumatoid arthritis, ARAVA acts as a so-called “disease-modifying antirheumatic drug (DMARD)” and improves the signs and symptoms of the disease.
ARAVA has immunomodulating/immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. In animal models of autoimmune diseases, leflunomide has been shown to give the best protection when administered in the early phase of the disease progression.
Leflunomide is absorbed almost completely, and converted rapidly to the active metabolite by first-pass metabolism in gut wall and liver. This metabolite is responsible for essentially all of the *in vivo* activity of ARAVA.
The occurrence of peak plasma concentrations of the active metabolite varies considerably, between 1 hour and 24 hours after single administration. Due to its very long half-life (approximately 2 weeks), a loading dose of 100mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state plasma concentrations of the active metabolite. Without a loading dose, it is estimated that attainment of steady state would require nearly two months of dosing.
The active metabolite is extensively bound to protein (albumin), thereby possibly leading to displacement of other highly-bound drugs. There is no indication that this effect is of clinical relevance.
Elimination of the active metabolite is slow and is characterized by an apparent clearance of approximately 31ml per hour. It was still detectable in urine and faeces 36 days after a single administration.
Administration of an oral suspension of activated powdered charcoal or cholestyramine leads to a rapid and significant increase in the elimination rate of the active metabolite and decline in plasma concentrations.
Consequently, where rapid elimination of this metabolite is necessary, any of these medicines may be used to carry out an elimination procedure as described below (see “Special warnings and precautions for use”).
The limited pharmacokinetic data available for the elderly are consistent with pharmacokinetics in younger adults. In patients with renal impairment, pharmacokinetic parameters gave no indication of accumulation.
No data are available regarding treatment of patients with hepatic impairment.

Indications
ARAVA is indicated for treatment of adult patients with:
1. Active rheumatoid arthritis to improve physical function,
2. Active psoriatic arthritis

Regarding the use of ARAVA in patients recently pre-treated with DMARDs (disease modifying antirheumatic drug) which are toxic for the liver (hepatotoxic) or for the blood (haematotoxic) and patients for whom substitution with another DMARD is planned, see “Special warnings and precautions for use”.
Switching from leflunomide to another DMARD without following the elimination procedure may also increase risk of serious adverse reactions even for a long time after switching.

Contraindications
ARAVA must not be taken by patients with
- Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients (see “Composition”)
- Hypersensitivity to teriflunomide
- Severe deficiency of the immune system (e.g. in AIDS)
- Significant impairment of the bone marrow function or a marked decrease in the number of red or white blood cells (anaemia or leucopenia/neutropenia) or of platelets (thrombocytopenia), due to causes other than rheumatoid or psoriatic arthritis
- Serious infections
- Impairment of liver function
- Severe excessive reduction in blood protein concentration (hypoproteinemia) due, e.g., to a certain renal disease (nephrotic syndrome).
- Moderate to severe renal insufficiency, since available clinical experience is insufficient
- In pregnant women or in women of child-bearing potential who do not use reliable contraception. This applies during treatment and after treatment discontinuation, as long as the plasma levels of the active metabolite are above 0.02mg/l (see “Pregnancy and lactation”). Pregnancy must be excluded before start of the treatment.
- In breast-feeding women since leflunomide and metabolites may pass into breast milk (see “Pregnancy and lactation”).

Special warnings and precautions for use
Before initiating treatment with Arava, careful consideration during the risk-benefit evaluation must be given to the possibility of increased side effects in patients recently pre-treating with hepatotoxic or haematotoxic DMARDs.

Treatment with ARAVA requires careful medical supervision.

- General: serious side effects (e.g. hepatotoxicity, haematotoxicity or allergic reactions) may occur or persist (see “Undesirable effects”) - given the long half-life of the active metabolite of leflunomide - even after treatment has been stopped. Therefore, when such effects occur, when any additive risks (i.e. kinetic interaction, organ toxicity) must be precluded, or when substitution with another DMARD (e.g. methotrexate) is planned, the following **elimination procedure** should be carried out: Administer cholestyramine (8 g three times daily) or alternatively, activated charcoal (powder made into a suspension, 50 g four times daily). The complete procedure usually takes 11 days, but may be modified depending on clinical or laboratory variables. For suspected severe immunologic/allergic reactions, more prolonged cholestyramine or activated charcoal administration may be necessary to achieve rapid and sufficient elimination.
Co-administration of teriflunomide with leflunomide is not recommended as leflunomide is the parent compound of teriflunomide.

- Liver: Since the active metabolite of leflunomide is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels are expected to be increased in patients with hypoproteinemia. ARAVA is contraindicated in patients with severe hypoproteinemia or liver impairment (see “Contraindications”). The use of leflunomide is not recommended in patients with evidence of infection with hepatitis B or C viruses.
For confirmed ALT elevation between 2and 3- fold the upper limit of normal, with a dose reduction from 20 to 10mg/day, administration of leflunomide may be continued under weekly monitoring. If nevertheless ALT elevations persist or if ALT elevations of more than 3-fold the upper limit of normal are present,

leflunomide should be discontinued and the elimination procedure described above should be implemented.
Rare cases of serious liver injury, in isolated cases with fatal outcome, have been reported during treatment with leflunomide. Adherence to the above mentioned monitoring measure is essential to avoid serious liver damage (See “Undesirable effects”).
AST and ALT as well as blood pressure must be checked before the start of leflunomide treatment and periodically thereafter. A complete blood cell count, including differential white blood cell and platelets, must be performed before start of and during leflunomide treatment (See “Monitoring Requirement”).

- Blood formation and immune systems: the risk of haematological disorders (typically manifested, e.g., by paleness, tiredness, increased proneness to infections or bruising) increased in patients with pre-existing anaemia, leucopenia and/or thrombocytopenia, as well as in those with impaired bone marrow function or in those at risk of bone marrow suppression. The blood picture (complete blood cell count, including differential white blood cell count and platelet count) must be monitored frequently in these patients. (See “Monitoring Requirement”) if such disorders occur, the above-mentioned elimination procedure should be considered. In the event of severe haematological reactions, including pancytopenia, Arava and any concomitant myelosuppressive medication must be discontinued and the elimination procedure initiated.

- Infections: medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections. Infections may be more severe in nature (see “Undesirable effects”). and may therefore require early and vigorous treatment. In the event that a serious infection occurs it may be necessary to interrupt leflunomide treatment and administer the elimination procedure as described above.
Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants.
The risk of tuberculosis should be considered. Before starting treatment, all patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

- Respiratory: interstitial lung disease has been reported rarely during treatment with leflunomide. The risk of its occurrence is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation as appropriate.

- Peripheral Neuropathy: Cases of peripheral neuropathy have been reported in patients receiving leflunomide. Most patients improved after discontinuation of leflunomide. However there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking leflunomide develops a peripheral neuropathy, consider discontinuing therapy and performing the drug elimination procedure (see “Special warnings and precautions for use”.

- Combination with other treatments: Combined use – in particular in long-term treatment – of Arava with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine) with gold salts (intramuscular or oral), or with D-penicillamine, azathioprine and other immunosuppressive medicines (including Tumour Necrosis Factor alpha-Inhibitors), has not been adequately studied up to now in randomized trials (with the exception of methotrexate, see “Interactions”). Since additive or even synergistic toxicity (e.g. hepatotoxicity of haematotoxicity) may occur, combination therapy with another DMARD (e.g. methotrexate) is not advisable.

- Skin and mucous membranes reactions: If ulcerative inflammations of the oral mucosa (ulcerative stomatitis) occur, Arava should be discontinued.
Severe, sometimes life-threatening bullous skin and mucous membrane reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms) have been reported (see “Undesirable effects”). Once skin and/or mucosal changes (e.g. in the mouth) occur

possibly indicating the development of such reactions, Arava and any other associated medicine must be discontinued and the above-mentioned elimination procedure initiated immediately. Complete elimination is essential, and treatment with Arava must not be resumed.
Pustular psoriasis and worsening of psoriasis have been reported after the use of leflunomide. Treatment withdrawal may be considered taking into account patient's disease and past history.

- Driving: Some adverse effects, such as dizziness, may impair the ability to concentrate and react, and therefore, constitute a risk in situations where these abilities are of particular importance (e.g., operating a vehicle or machinery).

- Blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

Fertility, Pregnancy and Lactation
ARAVA is contraindicated in pregnant women and pregnancy must be excluded before start of treatment.
In a small prospective study in women (n=64) who became inadvertently pregnant while taking leflunomide for no more than three weeks after conception and followed by a drug elimination procedure, no significant differences (p=0.13) were observed in the overall rate of major structural defects (5.4%) compared to either of the comparison groups (4.2% in the disease matched group [n=108] and 4.2% in healthy pregnant women [n=78]).
Lactation: Leflunomide or its metabolites may pass into breast milk. Breast-feeding women must, therefore, not receive ARAVA. (see "Contraindications").

Precautions and recommendations in conjunction with pregnancy and family planning
Based on available information, the risk of malformations in new-born infants of men taking Arava cannot be excluded. Men should be aware of such a risk and should not take Arava without using reliable contraceptive measures. To minimize any possible risk, men wishing to father a child should contact their doctor, who may advise that intake of Arava be discontinued and the above-mentioned elimination procedure be carried out for 11 days.
In women, sufficient elimination of this metabolite from the body prior to pregnancy is essential to avoid the risk of malformation in the infant. Therefore, women wishing to become pregnant who are taking Arava (or have taken it within the previous 2 years) must first speak with their doctor, who may advise – as a follow-on measure to the discontinuation of Arava - either implementing the elimination procedure (for 11 days as in the case of men) or waiting until two full years have elapsed.
In both sexes, sufficient elimination of active metabolites should subsequently be confirmed by two separate blood laboratory tests, the first to be carried out after conclusion of the elimination procedure – or, alternatively in the case of women, 2 years after discontinuation – and the second at least 14 days later. If both test values of active metabolites are below 0.02mg/l in blood plasma, the risk of malformation is very low.
If there is any delay in onset of the period or any other reason to suspect pregnancy, the doctor must be notified immediately and pregnancy testing carried out. If positive, the risk to the pregnancy must be discussed. Carrying out the elimination procedure at the first delay of the period may decrease the risk to the foetus from Arava.

Undesirable effects
Classification of expected frequencies:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon: (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Cardiac disorders
Common: mild increase in blood pressure;
Rare: severe increase in blood pressure
Not known: pulmonary hypertension

Blood and lymphatic system disorders
Common: Leukopenia (leukocytes > 2 G/l);

Uncommon: Anaemia, mild thrombocytopenia (platelets < 100 G/l);
Rare: Pancytopenia (probably by antiproliferative mechanism), Leukopenia (leukocytes < 2G/l), eosinophilia;
Very rare: agranulocytosis.
Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Nervous system
Common: paraesthesiae, headache, dizziness; weakness, peripheral neuropathy

Respiratory, thoracic and mediastinal disorders
Rare: interstitial lung disease (including interstitial pneumonitis), which may be fatal.

Gastrointestinal disorders
Common: diarrhea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain; colitis including microscopic colitis
Uncommon: taste disturbances;
Very rare: pancreatitis.

Renal and urinary disorders
Not known: Renal failure

Skin and subcutaneous tissue disorders
Common: increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin;
Uncommon: urticaria
Very rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Not known: cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see “Special warnings and precautions for use”).

Musculoskeletal system and connective tissue disorders
Common: tenosynovitis;
Uncommon: tendon rupture

Metabolism and nutritional disorders
Common: CPK increased
Uncommon: hypokalaemia, hyperlipidemia, hypophosphataemia
Rare: LDH increased;
Not known: hypouricemia

Infections and infestations
Rare: Severe infections and sepsis, which may be fatal
Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see also “Special warnings and precautions for use”). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplams benign, malignant and unspecified (incl cysts and polyps).
The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

General disorders and administration site conditions
Common: anorexia, weight loss (usually insignificant), asthenia

Immune system disorders
Common: mild allergic reactions
Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis

Hepatobiliary disorders
Common: elevation of liver parameters (transaminases [especially ALT]. less often gamma-GT, alkaline phosphatase, bilirubin)
Rare: hepatitis, jaundice/cholestasis
Very rare: severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Reproductive system and breast disorders
Not known: marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility

Pyschiatric disorders
Uncommon: anxiety

Interactions
Interactions studies have only been performed in adults.
- Recent or concomitant use of hepatotoxic or haematotoxic medicines – or immunosuppressive substances or the use of such following Arava treatment without a washout period – may lead to increased side effects.
- Methotrexate: Increase in liver enzymes was reported in clinical studies with co-administration of leflunomide and methotrexate. Therefore, liver enzymes should be monitored closely in the initial phase after a changeover to methotrexate has been demonstrated.
- Vaccinations: Since no clinical data are available on the efficacy and safety of concomitant vaccinations, live vaccines should not be administered during treatment and - after discontinuation of Arava - consideration should be given to the long half-life of leflunomide.
- Warfarin: There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered. Close INR follow-up and monitoring is recommended when warfarin is co-administered with leflunomide.
- Alcohol should be avoided during treatment, since additive hepatotoxic effects may occur.
- Cholestyramine and activated charcoal rapidly and significantly reduce the plasma concentration of the active metabolite of leflunomide and, hence, the effectiveness of Arava.
Furthermore, either may also influence the absorption of oestrogens and progestagens and, hence, the efficacy of oral contraceptives (to be noted in this regard is the fact that the efficacy of triphasic oral contraceptives is not influenced by leflunomide itself). Alternative contraceptive measures should be substituted for the duration of the above-mentioned elimination procedure (see “Special warnings and precautions for use”).
- Arava may influence the inactivation of certain other medicines metabolised by CYP2C9, an enzyme system of the liver. No safety problems, however, have been observed in combined use with medicines common in the treatment of rheumatoid arthritis (non-steroidal anti-inflammatory drugs, i.e. NSAIDs), whereas caution should be taken in combined use with other medicines metabolized by CYP2C9 (e.g., phenytoin, warfarin, tolbutamide, rifampicin).

Pharmacokinetic and pharmacodynamics interaction studies were conducted with the active metabolite of leflunomide (A771726). As similar drug-drug interactions cannot be excluded for leflunomide at recommended doses, the following recommendations should be considered in patients treated with leflunomide:
- Effect on CYP2C8 substrates: There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of A771726, suggesting that A771726 is an inhibitor or CYP2C8 *in vivo*. Therefore, monitoring patients with concomitant use of drugs metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, is recommended as they may have higher exposure.
- Effect on CYP1A2 substrates: Repeated doses of A771726 decreased C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55% respectively, suggesting that A771726 may be a weak inhibitor of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during concomitant treatment, as it could lead to the reduction of the efficacy of these products.

- Effect on organic anion transporter 3 (OAT3) substrates: There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of A771726, suggesting that A771726 is an inhibitor of OAT3 *in vivo*. Therefore, when co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.
- Effect on BCRP and/or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates: There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of A771726. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g. methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-CoA reductase inhibitors (e.g. simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.
- Effect on oral contraceptive (0.03 mg ethinylestradiol and 0.15 mg levonorgestrel): There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of A177276. While this interaction is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type of oral contraceptive treatment.
- Effect on warfarin: Repeated doses of A771726 had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 is not an inhibitor or inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when A771726 was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered, close INR follow-up and monitoring is recommended.

Dosage and administration

Dosage in adults above 18 years of age
Initiation of treatment by a physician experienced in the therapy of rheumatoid diseases and psoriatic arthritis is advisable. Special monitoring measures must be followed before initiation and during course of treatment (see “Monitoring Requirement”).
In rheumatoid arthritis: Leflunomide therapy is usually started with a loading dose of one ARAVA 100 mg tablet once daily for 3 days. The recommended maintenance dose is one ARAVA 10 mg tablet to one ARAVA 20 mg tablet once daily depending on the severity (activity) of the disease.
In psoriatic arthritis: leflunomide therapy is started with a loading dose of one ARAVA 100mg tablet once daily for 3 days. The recommended maintenance dose is one 20 mg once daily. An improvement in the rheumatoid condition usually occurs after 4 to 6 weeks and it may further improve up to 4 to 6 months. Treatment with non-steroidal anti-inflammatory drugs and/or corticosteroids may be continued when starting ARAVA.
No dosage adjustment recommended in patients with mild renal insufficiency. No dosage adjustment is required in patients above 65 years of age.
Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

Method of administration
ARAVA film-coated tablets should be swallowed without chewing and with a sufficient amount of liquid (approximately 1/2 glass).
They may be taken together with or independent of a meal.

Special populations
Leflunomide is not recommended in patients less than 18 years of age as it had not been studied in this age group.

Monitoring Requirement

Similar to other currently available medicines (e.g. methotrexate) for treatment of RA, patients on Arava will need to do some blood test during Arava treatment. This is to monitor their health conditions and to ensure that they are doing fine with the Arava treatment.
ALT (SGPT), AST and complete blood cell count, including differential white blood cell count & platelets, must be performed before start of leflunomide treatment & during treatment period.
The schedule of blood test for patients will be once every 2 weeks during the first six months of treatment. Subsequently, the frequency of the blood tests will be reduced to once in two months and thereafter.

Overdose
There have been reports of chronic overdose in patients taking ARAVA at daily dose up to five times the recommended daily dose and reports of acute overdose in adults or children. There were 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.

• Management
In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of the primary metabolite of leflunomide by approximately 40% in 24 hours and by 49 – 65% in 48 hours.
Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the primary metabolite of leflunomide by 37% in 24 hours and by 48% in 48 hours.
These washout procedures may be repeated if clinically necessary. Studies have shown that the primary metabolite of leflunomide is not dialyzable.

Storage
Please refer to outer packagingBlister packs: Store in the original package.
Bottles: Keep the container tightly closed.

Expiry date
Do not use later than the date of expiry stated on the outer packaging.

Keep medicines out of the reach of children.

Presentation
Arava **20**: 30 film-coated tablets in HDPE bottle.
Arava **100**: 3 film-coated tablets in aluminium blister pack
Not all presentations may be available locally.

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Date of revision of text
7 Jan 2020
References:
CCDS v20