PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

ARAVA 10 mg film-coated tablets.

ARAVA 20 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ARAVA 10 mg: Each film-coated tablet contains 10 mg leflunomide

ARAVA 20 mg: Each film-coated tablet contains 20 mg leflunomide

Contains sugar (lactose): ARAVA 10 mg contains 78 mg lactose monohydrate per tablet and ARAVA 20 mg contains 72 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

ARAVA 10 mg: white to almost white, round, film-coated tablets with a diameter of 7 mm. Embossment: ZBN.

ARAVA 20 mg: yellowish to ochre, spherical, triangular, film-coated tablets with a height of 7 mm. Embossment: ZBO.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ARAVA is indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic medicine (DMARD), and to improve physical function.

4.2 Posology and method of administration

Posology

ARAVA treatment should be initiated or prescribed by doctors experienced in the therapy of rheumatoid diseases.

For monitoring recommendations see section 4.4.

ARAVA therapy is started with a loading dose of 100 mg once daily for 3 days.

The recommended maintenance dose is ARAVA tablets 10 mg to 20 mg once daily.

A 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 dosage adjustment is required in patients above 65 years of age.

Administration: ARAVA tablets should be swallowed whole, with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

4.3 Contraindications

ARAVA must not be used in patients with hypersensitivity to leflunomide, the principal active metabolite teriflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients in the tablets.

ARAVA is contraindicated in:

- 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 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 nephritic 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. In animal studies leflunomide was teratogenic in rats and rabbits (see section 4.6).

Women must not breastfeed while they are receiving ARAVA.

Male patients should be aware of the possible male-mediated fetal toxicity. Reliable contraception during treatment with ARAVA should also be guaranteed.

ARAVA is not recommended for use in patients under 18 years as its safety and efficacy have not been studied in this age group.

4.4 Special warnings and precautions for use

Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side effects; therefore, the initiation of ARAVA treatment has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from ARAVA to another DMARD without a washout period may increase the possibility of additive risks of side effects for a long time after the switching.

General:

Due to the prolonged half-life (usually 1 to 4 weeks) of the active metabolite of ARAVA, adverse reactions may occur or persist even after ARAVA administration has been discontinued.
If a severe adverse reaction to ARAVA occurs (e.g. hepatotoxicity or haematotoxicity), or if for any other reason the primary metabolite needs to be cleared rapidly from the body (e.g. when switching to another DMARD (e.g. methotrexate) after treatment with ARAVA), a washout procedure as described below (and in section 4.9) has to be initiated and continued/repeated as clinically necessary. For suspected severe immunologic/allergic reactions, more prolonged colestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. For washout procedures in case of desired pregnancy, see section 4.6.

Recommendations for monitoring and washout procedures:

Monitoring recommendations:

ARAVA should be administered to patients only under careful medical supervision.

Latent or active tuberculosis:

Before starting treatment, all patients should be evaluated for active and inactive (latent) tuberculosis, as per locally approved guidelines on the diagnostic criteria for latent and active tuberculosis. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection (see Infections below).

Liver enzymes:

ALT (SGPT) must be checked before initiation of treatment and at least at monthly intervals during the first six months of treatment and every 6 – 8 weeks thereafter.

For confirmed ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may allow continued administration of leflunomide under close monitoring. If ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal persist or if confirmed ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide should be discontinued. Colestyramine or activated charcoal should be administered to more rapidly lower the levels of the active metabolite.

Blood pressure:

Blood pressure must be checked before the start of ARAVA treatment and periodically thereafter, as increases in blood pressure may occur.

Blood cell count:

A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of ARAVA treatment as well as monthly for the first 6 months of treatment and every 6 – 8 weeks thereafter.

Combinations with other treatments:

The use of ARAVA with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents (with the exception of methotrexate) has not been studied up to now.

The risk associated with combination therapy, in particular in long-term treatment, is unknown.

Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato- or haematotoxicity), combination with another DMARD (e.g. methotrexate) is not advisable.

Co-administration of teriflunomide with leflunomide is not recommended, as leflunomide is the parent compound of teriflunomide.

Switching to other treatments:

As ARAVA has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without a washout period may increase 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 medicines (e.g. methotrexate) may result in increased side effects; therefore, the initiation of ARAVA treatment has to be considered carefully regarding these benefit/risk aspects.

Washout procedure:

Colestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

Liver reactions:

Since the active metabolite of leflunomide (the primary metabolite) is highly protein bound and cleared via hepatic metabolism and biliary secretion, ARAVA should be used with caution in patients with impairment of liver function. Plasma levels of the primary metabolite are expected to be increased in patients with hypoproteinaemia or impairment of liver function. ARAVA is contraindicated in patients with severe hypoproteinaemia, impairment of liver function or pre-existing hepatic disease (see section 4.3).

Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with ARAVA.

Rare cases of serious liver injury, in isolated cases with fatal outcome, have been reported during treatment with ARAVA. Most of the cases occurred within the first 6 months of treatment. Although a causal relationship to ARAVA has not been established and multiple confounding factors were present in most cases, it is considered essential that monitoring recommendations (see above) are closely followed.

Haematological and immune system reactions:

In patients with pre-existing anaemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of

haematological disorders is increased. If such effects occur, a washout procedure (see above) to reduce plasma levels of the primary metabolite should be considered.

Frequent haematological monitoring (complete blood cell count, including differential white blood cell count and platelet count) should be performed in:

- **patients with recent or concomitant treatment with immunosuppressive or haematotoxic medicines, and when ARAVA treatment is followed by such substances without a washout period.**
- **patients with a history of relevant haematological abnormalities.**
- **patients with relevant haematological abnormalities at baseline due to causes other than rheumatoid arthritis.**

In case of severe haematological reactions, including pancytopenia, ARAVA and any concomitant myelosuppressive medication must be discontinued and an ARAVA washout procedure initiated.

Due to the potential for immunosuppression, although there is no clinical experience, ARAVA is not recommended in patients with:

- **severe immunodeficiency (e.g. AIDS)**
- **significant impairment of bone marrow function**
- **serious infections (see section 4.3).**

Skin reactions:

In case of ulcerative stomatitis, ARAVA administration should be discontinued. Cases of Stevens-Johnson syndrome or toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients treated with ARAVA (see section 4.8). As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, ARAVA and any other possibly associated medication must be discontinued, and an ARAVA washout procedure (see above) initiated immediately. A complete washout is essential in such cases and re-exposure to leflunomide is contraindicated (see section 4.3).

Infections:

Medicines like ARAVA that have immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections (see section 4.8). Infections may be more severe in nature and may therefore require early and vigorous treatment. In the event that

severe, uncontrolled infections occur, it may be necessary to stop ARAVA and administer a washout with colestyramine as described above.

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation (see *Monitoring recommendations* above).

Respiratory:

Interstitial lung disease has been reported rarely during treatment with ARAVA (see section 4.8). 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. Patients should be warned to report pulmonary symptoms, such as cough and dyspnoea, which should be further investigated to exclude interstitial lung disease. If interstitial lung disease is suspected, ARAVA should be discontinued and patients should be further investigated as appropriate.

Peripheral neuropathy:

Cases of peripheral neuropathy have been reported in patients receiving ARAVA. Most patients recovered after discontinuation of ARAVA, but 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 ARAVA develops a peripheral neuropathy, consider discontinuing therapy and performing the medicine washout procedure described above.

Renal impairment:

At present there is insufficient experience available to make specific dosage recommendations for patients with renal impairment. Caution should be used when administering ARAVA in this population. It should be considered that the active metabolite of ARAVA is highly protein bound.

Interactions:

Caution is advised when ARAVA is given together with medicines other than NSAIDs, metabolised by CYP2C9, such as warfarin (see section 4.5).

Procreation (recommendations for men):

There are no specific data on the risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimise any possible risk, men wishing to father a child should consider discontinuing use of ARAVA and taking colestyramine 8 g, three times daily for 11 days or 50 g of activated powdered charcoal, four times daily for 11 days. In either case the primary metabolite plasma concentration is then measured for the first time. Thereafter, the primary metabolite plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0,02 mg/L, and after a waiting period of at least 3 months, the risk of fetal toxicity is very low.

Hyperglycaemia and lactose intolerance:

ARAVA tablets contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. ARAVA 10 mg contains 78 mg lactose per tablet and ARAVA 20 mg contains 72 mg lactose per tablet.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take ARAVA.

4.5 Interaction with other medicines and other forms of interaction

Increased side effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol), haematotoxic or immunosuppressive substances. This is also to be considered when leflunomide treatment is followed by such substances without a washout period.

- **Methotrexate:** In a small (n=30) study with co-administration of ARAVA (10 mg to 20 mg per day) with methotrexate (10 mg to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both medicines and 3 after discontinuation of ARAVA. A more than 3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both medicines and 3 after discontinuation of ARAVA. Therefore, closer monitoring of liver enzymes is recommended in the initial phase after switching. Although a pharmacokinetic interaction with a BCRP substrate (rosuvastatin) was observed with the primary active metabolite of leflunomide (see below), no pharmacokinetic interaction between ARAVA (10 mg to 20 mg per day) (also a BCRP substrate) and methotrexate (10 mg to 25 mg per week) was demonstrated.

- **Vaccinations:** No clinical data is available on the efficacy and safety of vaccinations during ARAVA treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of ARAVA should be considered when contemplating administration of a live vaccine after stopping ARAVA.
- **Warfarin:** There have been case reports of increased prothrombin time when ARAVA and warfarin were co-administered. A pharmacodynamic interaction with warfarin was observed with the primary metabolite in a clinical pharmacology study (see below). Therefore, when warfarin is co-administered, close INR follow-up and monitoring is recommended.
- **NSAIDs:** In clinical trials no safety problems were observed when NSAIDs metabolised by CYP2C9, and ARAVA were co-administered. If the patient is already receiving nonsteroidal anti-inflammatory medicines (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide.
- The extent of ARAVA absorption is not affected when taken with food.
- No difference in clinical efficacy was seen between smokers and non-smokers.

Effect of other medicines on leflunomide:

CYP450 inhibitors and inducers:

- *In vitro* inhibition studies in human liver microsomes suggest that cytochrome P450 (CYP) 1A2, 2C19 and 3A4 are involved in leflunomide metabolism. An *in vivo* interaction study with leflunomide and cimetidine (non-specific weak cytochrome P450 (CYP) inhibitor) has demonstrated a lack of a significant impact on the primary metabolite.
- *Rifampicin:* Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer), the primary metabolite peak levels were increased by approximately 40 %, whereas the AUC was not significantly changed. The mechanism of this effect is unclear.

  The potential for ARAVA levels to continue to increase with multiple dosing may need to be considered if patients are to be receiving both ARAVA and rifampicin.
- *Colestyramine or activated charcoal:* Administration of colestyramine or activated charcoal leads to a rapid and significant decrease in plasma primary metabolite concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of the primary metabolite. ARAVA should not be given to patients using colestyramine.

Effect of leflunomide on other medicines:

- *Oral contraceptives: In vivo* medicine interaction studies have demonstrated a lack of significant medicine interaction between ARAVA and triphasic oral contraceptives. In a study in which ARAVA was given concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinylestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and the primary metabolite pharmacokinetics were within predicted ranges. A pharmacokinetic interaction with oral contraceptives was observed with the primary metabolite (see below).

The following pharmacokinetic and pharmacodynamic interaction studies were conducted with the principal active metabolite of leflunomide. As similar medicine-medicine interactions cannot be excluded for leflunomide at recommended doses, the following study results and recommendations should be considered in patients treated with leflunomide:

Effect on repaglinide (CYP2C8 substrate):

There was an increase in mean repaglinide Cmax and AUC (1,7- and 2,4-fold, respectively), following repeated doses of the primary metabolite, suggesting that the primary metabolite is an inhibitor of CYP2C8 *in vivo*. Therefore, monitoring patients with concomitant use of medicines metabolised by CYP2C8, such as repaglinide, paclitaxel or pioglitazone is recommended as they may have higher exposure.

Effect on caffeine (CYP1A2 substrate):

Repeated doses of the primary metabolite decreased the mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18 % and 55 %, respectively, suggesting that the primary metabolite may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine and theophylline) 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 Cmax and AUC (1,43- and 1,54-fold, respectively), following repeated doses of the primary metabolite, suggesting that the primary metabolite is an inhibitor of OAT3 *in vivo*. Therefore, when co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate and 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 Cmax and AUC (2,65- and 2,51-fold, respectively), following repeated doses of the primary metabolite. 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, 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 Cmax and AUC_{0-24} (1,58- and 1,54-fold, respectively) and levonorgestrel Cmax and AUC_{0-24} (1,33- and 1,41-fold, respectively) following repeated doses of the primary metabolite. 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 (CYP2C9 substrate):
Repeated doses of the active metabolite of ARAVA had no effect on the pharmacokinetics of *S*-warfarin, indicating that the primary metabolite is not an inhibitor or an inducer of CYP2C9. However, a 25 % decrease in peak international normalised ratio (INR) was observed when the primary metabolite was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered, close INR follow-up and monitoring is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

The active metabolite of leflunomide is teratogenic in rats and rabbits and it may cause fetal harm in humans. ARAVA must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with ARAVA and as long as the plasma levels of the active

metabolite are above 0,02 mg/L (see Washout procedure below). Pregnancy must be excluded before start of treatment with ARAVA.

Suspected pregnancy or women deciding to fall pregnant: Patients must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the doctor immediately for pregnancy testing, and if positive, the doctor and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite, by instituting the medicine elimination procedure described below, at the first delay of menses, may decrease the risk to the fetus from ARAVA.

Washout procedure: For women receiving ARAVA treatment and who wish to become pregnant, one of the following procedures is recommended:

- After stopping treatment with leflunomide, colestyramine 8 g is administered three times daily for a period of 11 days.
- After stopping treatment with leflunomide, 50 g of activated charcoal is administered four times daily for a period of 11 days.

The 11 days need not be consecutive unless there is a need to lower the primary metabolite plasma level rapidly. In either case, the primary metabolite plasma levels < 0,02 mg/L must be verified by two separate tests at least 14 days apart. Human plasma levels of the active metabolite less than 0,02 mg/L (0,02 µg/mL) are expected to have minimal risk based on available data.

Waiting period: Without the medicine elimination procedure, it may take up to 2 years to reach the primary metabolite levels of < 0,02 mg/L, due to individual variation in medicine clearance. However, also after such a waiting period, verification of the primary metabolite levels of < 0,02 mg/L by two separate tests at an interval of at least 14 days is required.

If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedure may be advisable. Reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated charcoal. Use of alternative contraceptive methods is recommended.

Lactation

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breastfeeding women must therefore not receive ARAVA.

4.7 Effects on ability to drive and use machines

ARAVA may cause side effects such as dizziness, which may affect the patient's ability to concentrate and react properly (see section 4.8). Patients should therefore be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: very common ≥ 1/10;

common ≥ 1/100 to < 1/10;

uncommon ≥ 1/1000 to < 1/100;

rare: ≥ 1/10 000 and < 1/1000;

very rare: ≤ 1/10 000

Not known (cannot be estimated from available data).

Infections and infestations:

Rare: severe infections and sepsis, which may be fatal

Immunosuppressive medications are known to increase susceptibility to infections, including opportunistic infections and infections with atypical organisms. In clinical studies, the incidence of, for example rhinitis and bronchitis (5 % vs 2 %), and pneumonia (3 % vs 0 %) was slightly increased in patients treated with ARAVA compared to placebo, whereas the overall incidence of infections was comparable to placebo.

Neoplasms benign and malignant (including cysts and polyps):

Not known: The risk of malignancy, particularly lymphoproliferative disorders, is also known to be increased with use of some immunosuppressive medicines

Blood and lymphatic system disorders:

Common: leucopenia with leucocyte count > 2 x 10^9/L (> 2 G/L)

Uncommon: anaemia, thrombocytopenia with platelet count < 100 x 10^9/L (< 100 G/L)

Rare: leucopenia with leucocyte count < 2 x 10^9/L (< 2 G/L), eosinophilia, pancytopenia

Very rare: agranulocytosis

Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects.

Immune system disorders:

Common: mild allergic reactions

Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotising vasculitis

Metabolism and nutrition disorders:

Uncommon: hypokalaemia

Not known: hyperlipidaemia, uric acid levels usually decrease due to a uricosuric effect

Possible further laboratory findings for which a clinical relevance could not be established include: small increases in LDH and creatine kinase (CK), and a small decrease in phosphate.

Psychiatric disorders:

Uncommon: anxiety

Nervous system disorders:

Common: headache, dizziness, paraesthesia

Uncommon: taste disturbances

Very rare: peripheral neuropathy

Cardiac disorders:

Common: increase in blood pressure

Rare: severe increase in blood pressure

Not known: pulmonary hypertension

Respiratory, thoracic and mediastinal disorders:

Rare: interstitial lung disease (including interstitial pneumonitis), which may be fatal

Gastrointestinal disorders:

Common: colitis including microscopic colitis, diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulcerations), abdominal pain

Very rare: pancreatitis

Hepatobiliary disorders:

Common: elevation of liver parameters (e.g. transaminase, 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

In clinical trials, ARAVA treatment was associated with elevations of liver enzymes (see section 4.4).

Skin and subcutaneous tissue disorders:

Common: rashes (including maculopapular rash), pruritus, eczema, dry skin, increased hair loss

Uncommon: urticaria

Very rare: Stevens-Johnson syndrome (erythema multiforme of major type), toxic epidermal necrolysis. In case reports received so far, a causal relationship with ARAVA treatment could not be established, but cannot be excluded

Not known: Cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, drug reaction with eosinophilia and systemic symptoms (DRESS), skin ulcer (see section 4.4)

Musculoskeletal, connective tissue and bone disorders:

Common: tenosynovitis

Uncommon: tendon rupture, has been reported as adverse events under treatment with leflunomide, however, a causal relationship could not be established

Renal and urinary disorders:

Not known: renal failure

Reproductive system and breast disorders:

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

General disorders and administration site conditions:

Common: weight loss, asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ARAVA is important. It allows continued monitoring of the benefit/risk balance of ARAVA. Health care professionals are asked to report any suspected adverse reactions to: The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256-3700 (tel), or SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There have been reports of accidental overdose in patients taking ARAVA at daily doses up to five times the recommended daily dose for several days 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 were consistent with the adverse effects profile for ARAVA. The most frequent adverse events observed were diarrhoea, abdominal pain, leucopenia, anaemia and elevated liver function tests.
In the event of relevant overdose or toxicity, colestyramine or charcoal must be given to accelerate elimination. Colestyramine 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 by approximately 40 % in 24 hours and by 49 % to 65 % in 48 hours.

Administration of activated charcoal, orally or via a nasogastric tube at a dose of 50 g every six hours for 24 hours, has been shown to reduce plasma concentrations of the active metabolite by 37 % in 24 hours and by 48 % in 48 hours.

The washout procedures may be repeated if clinically necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Leflunomide belongs to the medicine class A 3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA13.

Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in *de novo* pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.

5.2 Pharmacokinetic properties

Following oral administration, leflunomide is metabolised to the active primary metabolite that is responsible for essentially all of its activity *in vivo*. Plasma levels of leflunomide are occasionally seen at very low levels. Studies of the pharmacokinetics of leflunomide have primarily examined the plasma concentrations of this active metabolite.

Absorption: Following oral administration, peak levels of the primary metabolite occurred between 6 to 12 hours after dosing. Due to the very long half-life of the primary metabolite (approx. 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly 2 months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that the primary metabolite levels are dose proportional. Relative to an oral solution, leflunomide tablets are 80 % bioavailable. Co-administration of leflunomide tablets with a high-fat meal did not have a significant impact on the primary metabolite plasma levels.

Distribution: The primary metabolite has a low volume of distribution (Vss = 0,13 L/kg) and is extensively bound (> 99,3 %) to albumin in healthy subjects. Protein binding has been shown to be linear at therapeutic concentrations. The free fraction of the primary metabolite is slightly higher in patients with RA and approximately doubled in patients with chronic renal failure; the mechanism and significance of these increases are unknown.

Metabolism: Leflunomide is metabolised to one primary and many minor metabolites. Of these minor metabolites, only 4-trifluoromethylaniline (TFMA) is quantifiable, occurring at low levels in the plasma of some patients. The parent compound is rarely detectable in plasma. At the present time, the specific site of leflunomide metabolism is unknown. *In vivo* and *in vitro* studies suggest a role for both the GI wall and the liver in medicine metabolism. No specific enzyme has been identified as the primary route of metabolism for leflunomide; however, hepatic cytosolic and microsomal cellular fractions have been identified as sites of medicine metabolism.

Elimination: The primary metabolite is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. In a 28-day study of medicine elimination (n=3) using a single dose of radiolabelled compound, approximately 43 % of the total radioactivity was eliminated in the urine and 48 % was eliminated in the faeces. Subsequent analysis of the samples revealed the primary urinary metabolites to be leflunomide glucuronides and an oxanilic acid derivative of the primary metabolite. The primary faecal metabolite was the primary metabolite. Of these two routes of elimination, renal elimination is more significant over the first 96 hours, after which faecal elimination begins to predominate. In a study involving the intravenous administration of the primary metabolite, the clearance was estimated to be 31 mL/h. In small studies using activated charcoal or cholestyramine to facilitate medicine elimination, the *in vivo* plasma half-life of the primary metabolite was reduced from > 1 week to approximately 1 day. Similar reductions in plasma half-life were observed for a series of volunteers (n=96) enrolled in pharmacokinetic trials who were given colestyramine. This suggests that biliary recycling is a major contributor to the long elimination half-life of the primary metabolite. Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that the primary metabolite cannot be removed by dialysis**.**

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, maize starch, povidone.

Film coating: Hypromellose, macrogol 8000, talc and titanium dioxide. The 20 mg tablet also contains yellow ferric oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle tightly closed.

6.5 Nature and contents of container

ARAVA 10 mg: 30 tablets in plastic bottles.

ARAVA 20 mg: 30 tablets in plastic bottles.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

Telephone number: 011 256 3700

8 REGISTRATION NUMBERS

ARAVA 10 mg: 33/3.1/0290

ARAVA 20 mg: 33/3.1/0291

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 8 February 2002

10 DATE OF REVISION OF THE TEXT

28 January 2022

NAMIBIA
Scheduling status: NS2

Registration numbers:

ARAVA 10 mg: 04/3.1/1834

ARAVA 20 mg: 04/3.1/1383

BOTSWANA
Scheduling status: S2

Registration number:

ARAVA 20 mg: BOT0700974