1. Name of the medicinal product

Arava 10 mg film-coated tablets
Arava 20 mg film-coated tablets

2. Qualitative and quantitative composition

Each 10 mg tablet contains 10 mg of leflunomide.
Each 20 mg tablet contains 20 mg of leflunomide.

Excipients with known effect:
Each 10 mg tablet contains 78 mg of lactose monohydrate.
Each 20 mg tablet contains 72 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Arava 10 mg: White to almost white, round, film-coated tablet, imprinted with ZBN on one side.

Arava 20 mg: Yellowish to ochre and triangular film-coated tablet, imprinted with ZBO on one side.

Patient safety information Card
The marketing of ARAVA is subject to a risk management plan (RMP) including a 'Patient safety information card'.
The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

4. Clinical particulars

4.1 Therapeutic indications

Arava is indicated in adults for the treatment of active rheumatoid arthritis (RA):

1. to reduce signs and symptoms
2. to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing
3. to improve physical function.

Arava is indicated for the treatment of adult patients with active psoriatic arthritis.

4.2 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 (see section 4.4).

Posology

II 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 (see section 5.1).
The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.

I 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 (see section 5.1).

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 (see sections 5.1 and 5.2).

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.

4.3 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 listed in section 6.1.

- 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 (see section 4.4).

- 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 (see section 4.6). Pregnancy must be excluded before start of treatment with leflunomide.

- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Concomitant administration of hepatotoxic or haematotoxic DMARDs “disease-modifying antirheumatic drug" (e.g. methotrexate) is not advisable.
The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped. Therefore, when such toxicities occur or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary.

For washout procedures and other recommended actions in case of desired or unintended pregnancy, see section 4.6.

Liver reactions

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Co-treatment with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations are strictly adhered to.

ALT (SGPT) must be checked before initiation of leflunomide and at the same frequency as the complete blood cell count (every two weeks) during the first six months of treatment and every 8 weeks thereafter.

For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and wash-out procedures initiated. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

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

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients

with hypoproteinaemia. Arava is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Haematological reactions

Together with ALT, a complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter.

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 (see below) to reduce plasma levels of A771726 should be considered.

In case of severe haematological reactions, including pancytopenia, Arava and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated.

Combinations with other treatments

The use of leflunomide with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents including Tumour Necrosis Factor alpha-Inhibitors has not been adequately studied up to now in randomised trials (with the exception of methotrexate, see section 4.5). 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 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.

Skin reactions

In case of ulcerative stomatitis, leflunomide administration should be discontinued.

Very rare 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 leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, Arava and any other possibly associated treatment must be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contra-indicated (see section 4.3).

Haemophagocytic lymphohistiocytosis (HLH) / Macrophage activation syndrome (MAS):

Haemophagocytic lymphohistiocytosis (HLH), including macrophage activation syndrome (MAS), has been reported in patients treated with leflunomide.

Although rare, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with leflunomide may be complicated by HLH or MAS. Cases of HLH/MAS have also been reported independently of DRESS.

HLH/MAS is a serious and potentially life-threatening hyperinflammatory condition. Clinical features may include persistent fever, rash, neurological symptoms, hepatosplenomegaly, lymphadenopathy, cytopenias, markedly elevated serum ferritin, hypertriglyceridaemia, and abnormalities of liver function and coagulation.

Patients should be informed about the signs and symptoms associated with HLH/MAS and advised to seek medical attention immediately if such symptoms occur during leflunomide treatment.

If patients develop any of these conditions, stop leflunomide treatment and perform an accelerated drug elimination procedure (see section 4.4). Early recognition and prompt management are important to improve outcomes.

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.

Skin ulcers can occur in patients during therapy with leflunomide. If leflunomide-associated skin ulcer is suspected or if skin ulcers persist despite appropriate therapy, leflunomide discontinuation and a complete washout procedure should be considered. The decision to resume leflunomide following skin ulcers should be based on clinical judgement of adequate wound healing.

Impaired wound-healing after surgery can occur in patients during therapy with leflunomide. Based on an individual assessment, it may be considered to interrupt leflunomide treatment in the peri-surgical period and administer a washout procedure as described below. In case of interruption, the decision to resume leflunomide should be based on clinical judgment of adequate wound healing.

Musculoskeletal disorders

Myositis and /or rhabdomyolysis have been reported in patients treated with leflunomide, frequently in combination with other immunosuppressive drugs. Clinical symptoms may include unexplained muscle pain, tenderness or muscle weakness. Patients should be informed about the signs and symptoms associated with myositis and rhabdomyolysis and advised to seek medical attention immediately if such symptoms occur during leflunomide treatment. Monitor the patients for elevation of CK levels if clinically indicated. If patients develop any of these conditions, leflunomide must be discontinued and a washout procedure initiated (see section 4.4).

Infections

It is known that medicinal products with immunosuppressive properties - like leflunomide - may cause patients to be more susceptible to infections, including opportunistic infections. 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 interrupt leflunomide treatment and administer a washout procedure as described below.

Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants.

Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

Respiratory reactions

Interstitial lung disease, as well as rare cases of pulmonary hypertension and pulmonary nodules have been reported during treatment with leflunomide (see section 4.8). The risk of interstitial lung disease and pulmonary hypertension can be 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 Arava. Most patients improved after discontinuation of Arava. 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 Arava develops a peripheral neuropathy, consider discontinuing Arava therapy and performing the drug elimination procedure (see section 4.4).

Colitis

Colitis, including microscopic colitis has been reported in patients treated with leflunomide. In patients on leflunomide treatment presenting unexplained chronic diarrhoea appropriate diagnostic procedures should be performed.

Blood pressure

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

Procreation (recommendations for men)

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

There are no specific data on the risk of male-mediated foetal 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 leflunomide and taking colestyramine 8 g 3 times daily for 11 days or 50 g of activated powdered charcoal 4 times daily for 11 days.

In either case the A771726 plasma concentration is then measured for the first time. Thereafter, the A771726 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 foetal toxicity is very low.

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.

Lactose

Arava contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionised calcium analyser used (e.g. blood gas analyser). Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions studies have only been performed in adults.

Increased side effects may occur in case of recent or concomitant use of hepatotoxic or haematotoxic medicinal products or when leflunomide treatment is followed by such medicinal products without a washout period (see also guidance concerning combination with other treatments, section 4.4). Therefore, closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

Methotrexate

In a small (n=30) study with co-administration of leflunomide (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen on 5 of 30 patients. All elevations resolved, 2 with continuation of both medicinal products and 3 after discontinuation of leflunomide. A more than 3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both medicinal products and 3 after discontinuation of leflunomide.

In patients with rheumatoid arthritis, no pharmacokinetic interaction between the leflunomide (10 to 20 mg per day) and methotrexate (10 to 25 mg per week) was demonstrated.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations under leflunomide treatment. Vaccination with live attenuated vaccines is, however, not recommended. The long half-life of leflunomide should be considered when contemplating administration of a live attenuated vaccine after stopping Arava.

Warfarin and other coumarin anticoagulants

There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered. A pharmacodynamics interaction with warfarin was observed with A771726 in a clinical pharmacology study (see below). Therefore, when warfarin or another coumarin anticoagulant is co-administered, close international normalised ratio (INR) follow-up and monitoring is recommended.

NSAIDS/Corticosteroids

If the patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide.

Effect of other medicinal products on leflunomide:

Cholestyramine or activated charcoal

It is recommended that patients receiving leflunomide are not treated with colestyramine or activated powdered charcoal because this leads to a rapid and significant decrease in plasma A771726 (the active metabolite of leflunomide; see also section 5) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of A771726.

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 A771726 exposure. Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer) A771726 peak levels were increased by approximately 40%, whereas the AUC was not significantly changed. The mechanism of this effect is unclear.

Effect of leflunomide on other medicinal products:

Oral contraceptives

In a study in which leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinyloestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and A771726 pharmacokinetics were within predicted ranges. A pharmacokinetic interaction with oral contraceptives was observed with A771726 (see below).

The following pharmacokinetic and pharmacodynamic interaction studies were conducted with A771726 (principal active metabolite of leflunomide). As similar drug-drug 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 C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of A771726, suggesting that A771726 is an inhibitor of CYP2C8 *in vivo*. Therefore,

monitoring patients with concomitant use of medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, is recommended as they may have higher exposure.

Effect on caffeine (CYP1A2 substrate)
Repeated doses of A771726 decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that A771726 may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during 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 (Breast Cancer Resistance Protein) 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 A771726. 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 A771726 had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 is not an inhibitor or an 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Arava is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during and up to 2 years after treatment (see “waiting period” below) or up to 11 days after treatment (see abbreviated “washout period” below).

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician 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 drug elimination procedure described below, at the first delay of menses may decrease the risk to the foetus from leflunomide.

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]).

For women receiving leflunomide treatment and who wish to become pregnant, one of the following procedures is recommended in order to ascertain that the foetus is not exposed to toxic concentrations of A771726 (target concentration below 0.02 mg/L):

Waiting period

A771726 plasma levels 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.

After a 2-year waiting period, the A771726 plasma concentration is measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/L no teratogenic risk is to be expected.

For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Washout procedure

After stopping treatment with leflunomide:

• colestyramine 8 g is administered 3 times daily for a period of 11 days,

• alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

However, also following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation is required.

Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, prophylactic institution of a washout procedure may be advisable.

Both colestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Breast-feeding

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding women must, therefore, not receive leflunomide.

Fertility

Results of animal fertility studies have shown no effect on male and female fertility, but adverse effects on male reproductive organs were observed in repeated dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse effects with leflunomide are: mild increase in blood pressure, leucopenia, paraesthesia, headache, dizziness, 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)).

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.

Infections and infestations

Rare: severe infections, including sepsis which may be fatal.

Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see also section 4.4). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Blood and lymphatic system disorders

Common: leucopenia (leucocytes >2 G/L)

Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/L)

Rare:	pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes <2 G/L), eosinophilia
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 necrotizing vasculitis

Metabolism and nutrition disorders

Common:	CPK increased
Uncommon:	hypokalaemia, hyperlipidemia, hypophosphataemia
Rare:	LDH increased
Not known:	hypouricemia

Psychiatric disorders

Uncommon:	anxiety

Nervous system disorders

Common:	paraesthesia, headache, dizziness, peripheral neuropathy

Cardiac disorders

Common:	mild increase in blood pressure
Rare:	severe increase in blood pressure

Respiratory, thoracic and mediastinal disorders

Rare:	interstitial lung disease (including interstitial pneumonitis), which may be fatal
Not known:	pulmonary hypertension, pulmonary nodule

Gastrointestinal disorders

Common:	colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain,
Uncommon:	taste disturbances
Very rare:	pancreatitis

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

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), skin ulcer.

Musculoskeletal and connective tissue disorders

Common:	tenosynovitis
Uncommon:	tendon rupture

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:	anorexia, weight loss (usually insignificant), asthenia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at
https://sideeffects.health.gov.il/.

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking Arava at daily doses up to five times the recommended daily dose, and reports of acute overdose in adults and 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, diarrhoea, elevated liver enzymes, anaemia, leucopenia, pruritus and rash.

Management

In the event of an overdose or toxicity, colestyramine or charcoal is recommended 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 A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.

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.
These washout procedures may be repeated if clinically necessary.

Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that A771726, the primary metabolite of leflunomide, is not dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AK01.

Human pharmacology

Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties.

Animal pharmacology

Leflunomide is effective in animal models of arthritis and of other autoimmune diseases and transplantation, mainly if administered during the sensitisation phase. It has immunomodulating/ immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. Leflunomide exhibits the best protective effects on animal models of autoimmune diseases when administered in the early phase of the disease progression.
In vivo, it is rapidly and almost completely metabolised to A771726 which is active *in vitro*, and is presumed to be responsible for the therapeutic effect.

Mechanism of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.

Clinical efficacy and safety

Rheumatoid arthritis
The efficacy of Arava in the treatment of rheumatoid arthritis was demonstrated in 4 controlled trials (1 in phase II and 3 in phase III). The phase II trial, study YU203, randomised 402 subjects with active rheumatoid arthritis to placebo (n=102), leflunomide 5 mg (n=95), 10 mg (n=101) or 25 mg/day (n=104). The treatment duration was 6 months.
All leflunomide patients in the phase III trials used an initial dose of 100 mg for 3 days.
Study MN301 randomised 358 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=133), sulphasalazine 2 g/day (n=133), or placebo (n=92). Treatment duration was 6 months.
Study MN303 was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulphasalazine.
Study MN302 randomised 999 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was optional and only used in 10% of patients. Treatment duration was 12-months.

Study US301 randomised 482 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1 mg bid. Treatment duration was 12 months.

Leflunomide at a daily dose of at least 10 mg (10 to 25 mg in study YU203, 20 mg in studies MN301 and US301) was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis in all 3 placebo-controlled trials. The ACR (American College of Rheumatology) response rates in study YU203 were 27.7% for placebo, 31.9% for 5 mg, 50.5% for 10 mg and 54.5% for 25 mg/day. In the phase III trials, the ACR response rates for leflunomide 20 mg/day versus placebo were 54.6% versus 28.6% (study MN301), and 49.4% versus 26.3% (study US301). After 12 months with active treatment, the ACR response rates in leflunomide patients were 52.3% (studies MN301/303), 50.5% (study MN302) and 49.4% (study US301), compared to 53.8% (studies MN301/303) in sulphasalazine patients, 64.8% (study MN302), and 43.9% (study US301) in methotrexate patients. In study MN302 leflunomide was significantly less effective than methotrexate. However, in study US301 no significant differences were observed between leflunomide and methotrexate in the primary efficacy parameters. No difference was observed between leflunomide and sulphasalazine (study MN301). The leflunomide treatment effect was evident by 1 month, stabilised by 3 to 6 months and continued throughout the course of treatment.

A randomised, double-blind, parallel-group non-inferiority study compared the relative efficacy of two different daily maintenance doses of leflunomide, 10 mg and 20 mg. From the results, it can be concluded that efficacy results of the 20 mg maintenance dose were more favourable, on the other hand, the safety results favoured the 10 mg daily maintenance dose.

Paediatric population
Leflunomide was studied in a single multicenter, randomized, double-blind, active-controlled trial in 94 patients (47 per arm) with polyarticular course juvenile rheumatoid arthritis. Patients were 3–17 years of age with active polyarticular course JRA regardless of onset type and naive to methotrexate or leflunomide. In this trial, the loading dose and maintenance dose of leflunomide was based on three weight categories: <20 kg, 20-40 kg, and >40 kg. After 16 weeks treatment, the difference in response rates was statistically significant in favour of methotrexate for the JRA Definition of Improvement (DOI) ≥30% (p=0.02). In responders, this response was maintained during 48 weeks (see section 4.2). The pattern of adverse events of leflunomide and methotrexate seems to be similar, but the dose used in lighter subjects resulted in a relatively low exposure (see section 5.2). These data do not allow an effective and safe dose recommendation.

Psoriatic arthritis
The efficacy of Arava was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20 mg/day. Treatment duration was 6 months.

Leflunomide 20 mg/day was significantly superior to placebo in reducing the symptoms of arthritis in patients with psoriatic arthritis: the PsARC (Psoriatic Arthritis treatment Response Criteria) responders were 59% in the leflunomide group and 29.7% in the placebo group by 6 months (p<0.0001). The effect of leflunomide on improvement of function and on reduction of skin lesions was modest.

Postmarketing studies
A randomised study assessed the clinical efficacy response rate in DMARD-naïve patients (n=121) with early RA, who received either 20 mg or 100 mg of leflunomide in two parallel groups during the initial three day double blind period. The initial period was followed by an open label maintenance period of three months, during which both groups received leflunomide 20 mg daily. No incremental overall benefit was observed in the studied population with the use of a loading dose regimen. The safety data obtained from both treatment groups were consistent with the known safety profile of

leflunomide, however, the incidence of gastrointestinal adverse events and of elevated liver enzymes tended to be higher in the patients receiving the loading dose of 100 mg leflunomide.

5.2 Pharmacokinetic properties

Leflunomide is rapidly converted to the active metabolite, A771726, by first-pass metabolism (ring opening) in gut wall and liver. In a study with radiolabelled ^{14}C-leflunomide in three healthy volunteers, no unchanged leflunomide was detected in plasma, urine or faeces. In other studies, unchanged leflunomide levels in plasma have rarely been detected, however, at ng/ml plasma levels. The only plasma-radiolabelled metabolite detected was A771726. This metabolite is responsible for essentially all the *in vivo* activity of Arava.

Absorption

Excretion data from the ^{14}C study indicated that at least about 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 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 of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. In multiple dose studies in patients with rheumatoid arthritis, the pharmacokinetic parameters of A771726 were linear over the dose range of 5 to 25 mg. In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

In human plasma, A771726 is extensively bound to protein (albumin). The unbound fraction of A771726 is about 0.62%. Binding of A771726 is linear in the therapeutic concentration range. Binding of A771726 appeared slightly reduced and more variable in plasma from patients with rheumatoid arthritis or chronic renal insufficiency. The extensive protein binding of A771726 could lead to displacement of other highly-bound drugs. *In vitro* plasma protein binding interaction studies with warfarin at clinically relevant concentrations, however, showed no interaction. Similar studies showed that ibuprofen and diclofenac did not displace A771726, whereas the unbound fraction of A771726 is increased 2- to 3-fold in the presence of tolbutamide. A771726 displaced ibuprofen, diclofenac and tolbutamide but the unbound fraction of these medicinal products is only increased by 10% to 50%. There is no indication that these effects are of clinical relevance. Consistent with extensive protein binding A771726 has a low apparent volume of distribution (approximately 11 liters). There is no preferential uptake in erythrocytes.

Biotransformation

Leflunomide is metabolised to one primary (A771726) and many minor metabolites including TFMA (4-trifluoromethylaniline). The metabolic biotransformation of leflunomide to A771726 and subsequent metabolism of A771726 is not controlled by a single enzyme and has been shown to occur in microsomal and cytosolic cellular fractions. Interaction studies with cimetidine (non-specific cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer), indicate that *in vivo* CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

Elimination

Elimination of A771726 is slow and characterised by an apparent clearance of about 31 ml/hr. The elimination half-life in patients is approximately 2 weeks. After administration of a radiolabelled dose of leflunomide, radioactivity was equally excreted in faeces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and faeces 36 days after a single administration. The principal urinary metabolites were glucuronide products derived from leflunomide (mainly in 0 to 24-hour samples) and an oxanilic acid derivative of A771726. The principal faecal component was A771726.

It has been shown in man that administration of an oral suspension of activated powdered charcoal or colestyramine leads to a rapid and significant increase in A771726 elimination rate and decline in plasma concentrations (see section 4.9). This is thought to be achieved by a gastrointestinal dialysis mechanism and/or by interrupting enterohepatic recycling.

Renal impairment

Leflunomide was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of A771726 in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of A771726 was observed in haemodialysis subjects which was not due to extraction of medicinal product in the dialysate.

Hepatic impairment

No data are available regarding treatment of patients with hepatic impairment. The active metabolite A771726 is extensively protein bound and cleared via hepatic metabolism and biliary secretion. These processes may be affected by hepatic dysfunction.

Paediatric population

The pharmacokinetics of A771726 following oral administration of leflunomide have been investigated in 73 paediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) who ranged in age from 3 to 17 years. The results of a population pharmacokinetic analysis of these trials have demonstrated that paediatric patients with body weights ≤40 kg have a reduced systemic exposure (measured by C_{ss}) of A771726 relative to adult rheumatoid arthritis patients (see section 4.2).

Elderly

Pharmacokinetic data in elderly (>65 years) are limited but consistent with pharmacokinetics in younger adults.

5.3 Preclinical safety data

Leflunomide, administered orally and intraperitoneally, has been studied in acute toxicity studies in mice and rats. Repeated oral administration of leflunomide to mice for up to 3 months, to rats and dogs for up to 6 months and to monkeys for up to 1 month's duration revealed that the major target organs for toxicity were bone marrow, blood, gastrointestinal tract, skin, spleen, thymus and lymph nodes. The main effects were anaemia, leucopenia, decreased platelet counts and panmyelopathy and reflect the basic mode of action of the compound (inhibition of DNA synthesis). In rats and dogs, Heinz bodies and/or Howell-Jolly bodies were found. Other effects found on heart, liver, cornea and

respiratory tract could be explained as infections due to immunosuppression. Toxicity in animals was found at doses equivalent to human therapeutic doses.

Leflunomide was not mutagenic. However, the minor metabolite TFMA (4-trifluoromethylaniline) caused clastogenicity and point mutations *in vitro*, whilst insufficient information was available on its potential to exert this effect *in vivo*.

In a carcinogenicity study in rats, leflunomide did not show carcinogenic potential. In a carcinogenicity study in mice an increased incidence of malignant lymphoma occurred in males of the highest dose group, considered to be due to the immunosuppressive activity of leflunomide. In female mice an increased incidence, dose-dependent, of bronchiolo-alveolar adenomas and carcinomas of the lung was noted. The relevance of the findings in mice relative to the clinical use of leflunomide is uncertain.

Leflunomide was not antigenic in animal models.
Leflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range and exerted adverse effects on male reproductive organs in repeated dose toxicity studies. Fertility was not reduced.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core: Lactose monohydrate, maize starch, crospovidone, polyvidone K25, colloidal anhydrous silica, magnesium stearate.

Film coating: Methylhydroxypropylcellulose 5mPs, titanium dioxide (E171), talc, macrogol 8000.
Arava 20 mg also contains: yellow ferric oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25° C.
Keep the container tightly closed.

6.5 Nature and contents of container

30 or 100 film-coated tablets in a bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. Marketing authorisation holder and importer and its address

Sanofi Israel LTD., Greenwork Complex, P.O box 47, Yakum, ISRAEL

8. **License Number**

Arava 10 mg: 121-78-30132, Arava 20 mg: 121-79-30133

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