SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEFUNAR 10 mg film-coated tablets

LEFUNAR 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEFUNAR 10: Each film-coated tablet contains 10 mg leflunomide.

Excipient with known effect:

Contains sugar (lactose monohydrate), 80,00 mg per 10 mg film-coated tablet.

Contains lecithin (derived from soybeans), 0,06 mg per 10 mg film-coated tablet.

LEFUNAR 20: Each film-coated tablet contains 20 mg leflunomide.

Excipient with known effect:

Contains sugar (lactose monohydrate), 160,00 mg per 20 mg film-coated tablet.

Contains lecithin (derived from soybeans), 0,12 mg per 20 mg film-coated tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

LEFUNAR 10: White to off-white, round, biconvex film-coated tablets.

LEFUNAR 20: White to off-white, round, biconvex film-coated tablets with one-sided break-mark.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

LEFUNAR treatment should be initiated by medical practitioners experienced in the therapy of rheumatoid diseases.

For monitoring recommendations refer to section 4.4.

Posology

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

The recommended maintenance dose is LEFUNAR 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.

Paediatric population

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

Method of administration

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

4.3 Contraindications

LEFUNAR must not be used in patients with hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients listed in section 6.1.

LEFUNAR 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, leukopenia, 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 nephrotic syndrome.
- Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with LEFUNAR 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 LEFUNAR. In animal studies leflunomide was teratogenic in rats and rabbits.
- Breastfeeding women.
- Patients under 18 years as its safety and efficacy has not been studied in this age group.

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

4.4 Special warnings and precautions for use

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable.

The initiation of treatment with LEFUNAR has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from LEFUNAR to another DMARD without a washout period may increase the possibility of additive risks of side-effects for a long time after the switching.

The active metabolite of leflunomide, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, hematotoxicity or allergic reactions, see below), even if the treatment with LEFUNAR has been stopped. Therefore, when such toxicities occur or if for any other reason the active metabolite needs to be cleared rapidly from the body (e.g. when switching to another DMARD after treatment with LEFUNAR), the washout procedure, as prescribed below and in section 4.9, has to be followed. The procedure may be repeated as clinically necessary.

For suspected severe immunologic/ allergic reactions, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. For washout procedures and other recommended actions in case of desired or unintended pregnancy, refer to section 4.6.

Recommendations for monitoring and washout procedures:

Monitoring recommendations:

LEFUNAR 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 LEFUNAR 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, LEFUNAR should be discontinued and washout procedures initiated.

It is recommended that monitoring of liver enzymes be maintained after discontinuation of LEFUNAR 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, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of active metabolite are expected to be increased in patients with hypoproteinaemia. LEFUNAR is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Cholestyramine or activated charcoal should be administered to lower the levels of the active metabolite more rapidly.

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

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

Washout procedure

Cholestyramine 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.

Combinations with other treatments

The use of LEFUNAR with antimalarials used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive medicines (with the exception of methotrexate) including Tumour Necrosis Factor Alpha Inhibitors 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

Switching from LEFUNAR to another DMARD (e.g. methotrexate) without a washout period may increase the possibility of additive risks of side effects 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 LEFUNAR treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

Liver reactions

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. Concomitant treatment with other hepatotoxic medicines were frequently present. It is considered essential that monitoring recommendations are strictly adhered to (see ‘Monitoring Recommendations’ above).

It is recommended that monitoring of liver enzymes be maintained after discontinuation of LEFUNAR 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 LEFUNAR.

Since the active metabolite of leflunomide, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of the active metabolite are expected to be increased in patients with hypoproteinaemia. LEFUNAR 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 LEFUNAR treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter.

Frequent haematological monitoring should be performed in:

- Patients with recent or concomitant treatment with immunosuppressive or haematotoxic medicines, and when leflunomide 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 patients with pre-existing anaemia, leukopenia, 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 above) to reduce plasma levels of the primary metabolite should be considered.

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

Due to the potential for immunosuppression, although there is no clinical experience

leflunomide is contraindicated 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, LEFUNAR 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 leflunomide (see section 4.8). As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, LEFUNAR and any other possibly associated treatment must be discontinued, and a LEFUNAR washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to LEFUNAR is contraindicated (see section 4.3).

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 judgment of adequate wound healing.

Infections

It is known that medicines with immunosuppressive properties, like LEFUNAR, 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 LEFUNAR treatment and administer a washout procedure as described above.

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 cases of pulmonary hypertension have been reported during treatment with leflunomide (see section 4.8). The risk of their occurrence 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 leflunomide. Most patients improved after discontinuation of leflunomide. However, there was a wide variability in final outcome, 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 LEFUNAR develops a peripheral neuropathy, consider discontinuing LEFUNAR therapy and performing the washout procedure.

Colitis

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

Blood pressure

Blood pressure must be checked before the start of LEFUNAR 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 LEFUNAR 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 LEFUNAR and taking cholestyramine 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 plasma concentration of the active metabolite is then measured for the first time and 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.

Interactions

Caution is advised when LEFUNAR is given together with medicines, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide (see section 4.5)

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 LEFUNAR in this population. It should be considered that the active metabolite of leflunomide is highly protein bound.

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with LEFUNAR 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 LEFUNAR or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

Lactose

LEFUNAR contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LEFUNAR.

Lecithin

LEFUNAR contains lecithin, derived from soybeans. If you are allergic to peanut or soya, do not use this medicine.

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 LEFUNAR treatment is followed by such substances without a washout period.

Methotrexate

Reports of studies have shown that co-administration of leflunomide and methotrexate caused elevation in liver enzymes.

Closer monitoring of liver enzymes is recommended in the initial phase after switching. In patients with rheumatoid arthritis, no pharmacokinetic interaction between leflunomide 10 mg to 20 mg per day) and methotrexate (10 mg 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 LEFUNAR should be considered when contemplating administration of a live attenuated vaccine after stopping LEFUNAR.

Warfarin and other coumarin anticoagulants

Increased prothrombin time, when leflunomide and warfarin were co-administered, have been reported. A pharmacodynamics interaction with warfarin was observed with the primary metabolite. 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 medicines on LEFUNAR

Cholestyramine or activated charcoal

It is recommended that patients receiving LEFUNAR are not treated with cholestyramine or activated powdered charcoal because this leads to a rapid and significant decrease in plasma concentrations of the active metabolite of leflunomide . The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of the active metabolite.

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. Reports of an *in vivo* interaction study with cimetidine (non-specific cytochrome P450 inhibitor) has demonstrated a lack of a significant interaction.

It has been reported that following concomitant administration of a single dose of leflunomide 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 LEFUNAR levels to continue to increase with multiple dosing may need to be considered if patients are to be receiving both LEFUNAR and rifampicin.

Phenytoin, tolbutamide, warfarin and many NSAIDs are metabolised by cytochrome P450 2C9 (CYP2C9). Reports on *in vitro* studies indicate that the primary metabolite inhibits CYP2C9 activity. The clinical significance of this finding with regard to phenytoin and tolbutamide is unknown.

Caution is advised when these medicines are given in combination. In clinical trials no safety problems were observed when NSAIDs metabolised by CYP2C9, and leflunomide were co-administered. There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered.

Effect of LEFUNAR on other medicines

Oral contraceptives

Studies have shown no significant interaction between leflunomide and triphasic oral contraceptives.

Studies have shown an increase in mean ethinylestradiol and levonorgestrel following repeated doses of the leflunomide active 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.

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

Effect on CYP2C8 substrates

Monitoring patients with concomitant use of medicines metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, is recommended as they may have higher exposure to these medicines.

Effect on CYP1A2 substrates

Medicines 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 medicines.

Effect on organic anion transporter 3 (OAT3) substrates

Caution is recommended when co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate or zidovudine as the levels of these medicines may be increased.

Effect on BCRP (Breast Cancer Resistance Protein) and /or organic anion transporting polypeptide B1 and B3(OATP1B1/B3) substrates

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 these medicines and reduction of the dose of these medicines should be considered.

The extent of LEFUNAR absorption is not affected when taken with food.

No difference in clinical efficacy was seen between smokers and non-smokers.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

LEFUNAR must not be given to women of childbearing potential who are not using reliable contraception during treatment with LEFUNAR and as long as the plasma levels of the active metabolite are above 0,02 mg/L (see Waiting period and Washout procedure below). Pregnancy must be excluded before start of treatment with LEFUNAR.

Pregnancy

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

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 medical practitioner immediately for pregnancy testing, and if positive, the medical practitioner 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 foetus from LEFUNAR.

For women receiving LEFUNAR 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 the active metabolite of leflunomide (target concentration below 0,02 mg/L):

Waiting period:

Active metabolite 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 LEFUNAR.

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 both plasma concentrations are below 0,02 mg/L minimal risk is expected, based on available data.

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 cholestyramine or activated charcoal. Use of alternative contraceptive methods is recommended.

Washout procedure:

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

- after stopping treatment with LEFUNAR, cholestyramine 8 g is administered three times daily for a period of 11 days.

- after stopping treatment with LEFUNAR, 50 g of activated powdered 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 levels 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.

Breastfeeding

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Women breastfeeding their babies must therefore not receive LEFUNAR.

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.

4.7 Effects on ability to drive and use machines

Since adverse reactions such as dizziness have been reported in patients receiving leflunomide, patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that LEFUNAR does not adversely affect performance.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse effects with leflunomide are: mild increase in blood pressure, leukopenia, 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)).

b) Tabulated list of adverse reactions

Infections and infestations	
Less frequent:	Severe infections, including sepsis which may be fatal. Leflunomide may increase susceptibility to infections, including opportunistic infections (see section 4.4). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).
Neoplasms, benign and malignant (incl. cysts and polyps):	
Frequency unknown:	The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive medicines.
Blood and lymphatic system disorders	
Frequent:	Leukopenia (leucocytes >2 G/L)
Less frequent:	Anaemia, mild thrombocytopenia (platelets <100 G/L), pancytopenia (probably by antiproliferative mechanism), leukopenia (leucocytes <2 G/L), eosinophilia, agranulocytosis
Concomitant or consecutive use of potentially myelotoxic medicines may be associated with a higher risk of haematological effects.	
Immune system disorders	

Frequent:	Mild allergic reactions
Less frequent:	Severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotising vasculitis.
Metabolism and nutrition disorders	
Frequent:	CPK increased
Less frequent:	Hypokalaemia, hyperlipidaemia, hypophosphatemia, increased LDH
Frequency unknown:	Hypouricemia
Psychiatric disorders	
Less frequent:	Anxiety
Nervous system disorders	
Frequent:	Paraesthesia, headache, dizziness, peripheral neuropathy
Cardiac disorders	
Frequent:	Mild increase in blood pressure
Less frequent:	Severe increase in blood pressure
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Interstitial lung disease (including interstitial pneumonitis), which may be fatal.
Frequency unknown:	Pulmonary hypertension
Gastrointestinal disorders	
Frequent:	Colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain
Less frequent:	Taste disturbances, pancreatitis
Hepatobiliary disorders	

Frequent:	Elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)
Less frequent:	Hepatitis, jaundice/cholestasis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal
Skin and subcutaneous tissue disorders	
Frequent:	Increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin
Less frequent:	Urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Frequency unknown:	Cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), skin ulcer
Musculoskeletal, connective tissue and bone disorders	
Frequent:	Tenosynovitis
Less frequent:	Tendon rupture
Renal and urinary disorders	
Frequency unknown:	Renal failure
Reproductive system and breast disorders	
Frequency unknown:	Marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility
General disorders and administration site conditions	
Frequent:	Anorexia, weight loss (usually insignificant), asthenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions

to 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

Symptoms

There have been reports of accidental overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose for several days, and reports of acute overdose in adults and children. There were no side effects reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for LEFUNAR were: abdominal pain, nausea, diarrhoea, elevated liver enzymes, anaemia, leukopenia, pruritus and rash.

Management

In the event of an overdose or toxicity, cholestyramine or 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 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 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) have shown that the primary metabolite of LEFUNAR, is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AA13.

Leflunomide is an isoxazole immunomodulatory medicine 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.

Biotransformation

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 cholestyramine. 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

Tablet cores:

Low-substituted hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Sodium laurilsulfate

Tartaric acid

Film-coating: Opadry AMB white consisting of:

Lecithin

Poly(vinyl alcohol)

Talc

Titanium dioxide

Xanthan gum.

6.2 Incompatibilities

No incompatibilities

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original container until required for use.

6.5 Nature and contents of container

LEFUNAR 10 mg film-coated tablets are packed in white round or square HDPE bottles closed with white PP closures with desiccant insert.

LEFUNAR 20 mg film-coated tablets are packed in white round or square HDPE bottles closed with white PP closures with desiccant insert.

Pack sizes: 30 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.,

Block K West, Central Park

400 16th Road, Randjespark

Midrand

1685

8. REGISTRATION NUMBER(S)

LEFUNAR 10: 56/3.1/0178.176

LEFUNAR 20: 56/3.1/0179.177

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2024

10. DATE OF REVISION OF THE TEXT

19 March 2024