**PROFESSIONAL INFORMATION**

**LEFLUNOMIDE 20 UNICORN**

## SCHEDULING STATUS

Schedule 4.

## 1. NAME OF THE MEDICINE

LEFLUNOMIDE 20 UNICORN (20 mg leflunomide) film coated tablets.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LEFLUNOMIDE 20 UNICORN

Each tablet contains 20 mg leflunomide.

Contains sugar (lactose monohydrate 72 mg/tablet).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

LEFLUNOMIDE 20 UNICORN: Round convex, yellow film-coated tablets, scored in one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

LEFLUNOMIDE UNICORN is indicated for:

- 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

LEFLUNOMIDE 20 UNICORN treatment should be initiated by medical practitioners experienced in the therapy of rheumatoid diseases.

For monitoring recommendations refer to Warnings (see sections 4.4).

**Posology**

LEFLUNOMIDE 20 UNICORN therapy is started with a loading dose of 100 mg once daily for 3 days.

The recommended maintenance dose is leflunomide 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.

*Renal impairment*

There is no dose adjustment recommended in patients with mild renal insufficiency.

*Elderly population*

No dosage adjustment is required in patients above 65 years of age.

**Method of administration**

LEFLUNOMIDE 20 UNICORN 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 to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), teriflunomide or to any of the inactive ingredients of leflunomide.
- Liver function impairment.
- Severe immunodeficiency state, e.g. AIDS.

- Due to causes other than rheumatoid or psoriatic arthritis, patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia.
- Serious infections.
- As insufficient clinical experience is available in this group, patients with moderate to severe renal insufficiency.
- Severe hypoproteinaemia, e.g. in nephritic syndrome.
- Women who are pregnant 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. Animals studies have shown that leflunomide was teratogenic in rats and rabbits.
- During breast-feeding.
- Reliable contraception during treatment with LEFLUNOMIDE 20 UNICORN should be guaranteed as male patients should be aware of the possibility of male-mediated foetal toxicity.
- In children under 18 years as its safety and efficacy has not been established in this age group.

## 4.4 Special warnings and precautions for use

The concomitant use of hepatotoxic or haematotoxic (e.g. methotrexate) is not advisable as this may result in increased side-effects. Thus, the initiation of LEFLUNOMIDE 20 UNICORN should be carefully considered. A washout procedure should be followed after switching from LEFLUNOMIDE 20 UNICORN to another DMARD as an increase in the possibility of addictive risks of side-effects for a long time after the switching may occur, section 4.6.

*Liver reactions*

There have been reports of cases of severe liver injury, including cases with fatal outcome during treatment with leflunomide mostly within the first six months. Co-treatment with hepatotoxic medicinal products was frequently present. Essential monitoring is recommended.

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

Dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly for all ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal dose. Leflunomide must be discontinued and wash-out procedures initiated, 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 present. Until liver enzymes has normalised, monitoring of liver enzymes must be maintained after discontinuation.

It is recommended that the use of alcohol be avoided during treatment with leflunomide due to a potential for addictive hepatotoxic effects.

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. LEFLUNOMIDE 20 UNICORN is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

*Haematopoietic and immune system*

The risk for occurrence of haematological reactions is increased 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.

Complete blood cell count, including differential white blood cell count and platelet count should be monitored in:

- patients recently or concomitantly treated with immunosuppressive or haematotoxic medicines, and when LEFLUNOMIDE 20 UNICORN 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.

LEFLUNOMIDE 20 UNICORN and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated in case of severe haematological reactions, including pancytopenia.

Although there is no clinical experience, due to the potential for immunosuppression, LEFLUNOMIDE 20 UNICORN is not recommended in patients with:

- severe immunodefiency (e.g. AIDS)
- significant impairment of bone marrow function
- serious infections.

*Combinations with other treatments*

In randomised trials (with the exception of methotrexate, see section 4.5) the use of leflunomide with antimalarial medicines used in rheumatic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive medicines including Tumour Necrosis Factor alpha-Inhibitors has not been adequately studied up to now. The risk associated with combination therapy, in particular in long-term treatment, is unknown. Combination with another DMARD (e.g. methotrexate) is not advisable since such therapy can lead to addictive or even synergistic toxicity (e.g. hepato- or haematotoxicity). As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended.

*Switching to other treatments*

Switching to another DMARD (e.g. methotrexate) without performing the washout procedure referred to below, may raise the possibility of addictive risks even for a long time after the switching (i.e. kinetic interaction, organ toxicity) as leflunomide has a long persistence in the body.

*Skin reactions*

Leflunomide treatment should be discontinued in case of ulcerative stomatitis.

Patients treated with leflunomide have reported cases of Steven Johnson syndrome or toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

LEFLUNOMIDE 20 UNICORN and other possibly associated treatment must be discontinued, and leflunomide washout procedure initiated immediately, as soon as skin and/or mucosal reactions are observed which raises the suspicion of severe reactions. A complete washout is essential in such cases and re-exposure to leflunomide is contraindicated.

After the use of leflunomide, pustular psoriasis and worsening of psoriasis have been reported. Depending on the patient's disease and past history, treatment withdrawal may be considered.

*Infections*

Medications with immunosuppressive properties like leflunomide, may cause patients to be more susceptible to infections, including opportunistic infections. Infections may require early and vigorous treatment as it may be more severe in nature. It may be necessary to interrupt LEFLUNOMIDE 20 UNICORN treatment and administer a washout period on the event of a serious infection.

Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

*Respiratory reactions*

During treatment of leflunomide, interstitial lung disease, as well as rare cases of pulmonary hypertension (see section 4.8). In patients with a history of interstitial lung disease, the risk of their occurrence can be increased. Interstitial lung disease, a potentially fatal disorder, may occur acutely during treatment. Reasons for discontinuation and further investigation may include pulmonary symptoms such as cough and dyspnoea.

*Peripheral neuropathy*

Patients receiving LEFLUNOMIDE 20 UNICORN have reported cases of peripheral neuropathy. After discontinuation of LEFLUNOMIDE 20 UNICORN, most patients improved but some patients had persistent symptoms. Concomitant neurotoxic medications and diabetes may increase the risk for peripheral neuropathy after the age of 60. Discontinuation of LEFLUNOMIDE 20 UNICORN and performing the drug elimination procedure (see section 4.4) should be considered if a patient taking LEFLUNOMIDE 20 UNICORN develops a peripheral neuropathy.

*Colitis*

Patients treated with leflunomide have reported colitis, including microscopic colitis. Patients being treated with leflunomide presenting unexplained chronic diarrhoea appropriate diagnostic procedures should be performed.

*Blood pressure*

Before initiating treatment with leflunomide and periodically thereafter, blood pressure must be checked.

*Procreation (recommendation for men)*

Awareness of possible male-mediated foetal toxicity should be advised to male patients. During treatment with leflunomide, reliable contraception should be guaranteed.

Animal studies to evaluate the risk of male-mediated foetal toxicity have not been conducted therefore there is no specific data on this risk. Men wanting to father a child should consider discontinuation of leflunomide and taking cholestyramine 8 g 3 times a day for 11 days or 50 g of activated powdered charcoal 4 times a day for 11 days.

In either case, the primary metabolite plasma concentration is the measured for the first time. Thereafter, the primary metabolite plasma concentration must be determined again after an interval of at least 14 days. After a waiting period of at least 3 months and if both plasma concentrations are below 0,02 mg/l, the risk of foetal toxicity is very low.

*Washout procedure*

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

*Interference with determination of ionised calcium levels*

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), the measurement of ionised calcium levels might show falsely decreased values. Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. It is recommended to determine the total albumin adjusted serum calcium concentration in in case of doubtful measurements.

***Information of excipients of LEFLUNOMIDE 20 UNICORN***

LEFLUNOMIDE 20 UNICORN contains sugar (lactose monohydrate). Patients with the rare hereditary conditions of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take LEFLUNOMIDE 20 UNICORN.

## 4.5 Interaction with other medicines and other forms of interaction

Interactions studies have only been performed in adults.

In the case of recent or concomitant use of hepatotoxic (including alcohol), haematotoxic or immunosuppressive substances, increased side-effects may occur. This may also occur when leflunomide treatment is followed by such substances without a washout period.

*Methotrexate*

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

No pharmacokinetic interaction between leflunomide (10 to 20 mg) and methotrexate (10 to 25 mg) was demonstrated in patients with rheumatoid arthritis.

*Vaccination*

No data is available on safety and efficacy of vaccinations under leflunomide treatment therefore vaccination with live attenuated vaccines is not recommended. After stopping LEFLUNOMIDE 20 UNICORN treatment, the long half-life of leflunomide should be considered when contemplating administration of a live attenuated vaccine.

*Warfarin and other coumarine anticoagulants*

When using leflunomide and warfarin concomitantly, there have been case reports of increased prothrombin time. In a clinical pharmacology study, a pharmacodynamics interaction with warfarin and teriflunomide was observed. Close international normalised ration (INR) follow-up and monitoring is recommended when warfarin and another coumarin anticoagulant is co-administered.

*NSAIDs/Corticosteroids*

If a patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, they may continue the treatment after starting leflunomide.

***Effects of other medicinal products 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 LEFLUNOMIDE 20 UNICORN 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 LEFLUNOMIDE 20 UNICORN levels to continue to increase with multiple dosing may need to be considered if patients are to be receiving both LEFLUNOMIDE 20 UNICORN and rifampicin.
- *Cholestyramine or activated charcoal*: Administration of cholestyramine 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. LEFLUNOMIDE 20 UNICORN should not be given to patients using cholestyramine.

***Effects of leflunomide on other medicines:***

*Oral contraceptives*

Studies have demonstrated a lack of significant interaction between LEFLUNOMIDE 20 UNICORN and triphasic oral contraceptives as there was no reduction in in contraceptive activity of the pill and the primary metabolite pharmacokinetics were within predicted ranges.

*The following pharmacokinetic and pharmacodynamic interactions were conducted with the primary metabolite. As similar 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 $C_{max}$ and AUC (1.7- and 2.4-fold, respectively), following repeated doses of 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, pioglitazone or rosiglitazone, is recommended as they may have higher exposure.

*Effect on caffeine (CYP1A2 substrate)*

Repeated doses of the primary metabolite decreased mean $C_{max}$ 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, 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 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 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, 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 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, 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 medicines and reduction of the dose of these medicines 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 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 primary metabolite 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

*Women of childbearing potential/ female and male contraception*

LEFLUNOMIDE 20 UNICORN must not be administered to women of childbearing age who are not using a reliable contraceptive during treatment with LEFLUNOMIDE 20 UNICORN and for a certain period of time thereafter, see washout procedure.

*Pregnancy*

LEFLUNOMIDE 20 UNICORN must not be administered to pregnant women. Before starting treatment with LEFLUNOMIDE 20 UNICORN, pregnancy must be excluded.

Medical practitioners must advise patients to immediately notify for pregnancy testing if there is any delay in the onset of their menstrual cycle or any other reason to suspect pregnancy. If positive, the medical practitioner and patient must discuss the risk of pregnancy. It is possible that rapidly lowering the blood level of the active metabolite, by performing the washout procedure at the first delay of the menstrual cycle, may decrease the risk to the foetus from LEFLUNOMIDE 20 UNICORN.

*Washout procedure:* Women wishing to become pregnant whilst receiving LEFLUNOMIDE 20 UNICORN treatment, the following procedures are recommended:

- Cholestyramine 8 g is administered 3 times daily for a period of 11 days after stopping treatment with leflunomide
- 50 g activated charcoal is administered four times daily for a period of 11 days after stopping treatment with leflunomide.

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.

Without the washout 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 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.

*Lactation*

Studies have indicated that leflunomide or its metabolites is secreted in breast milk therefore LEFLUNOMIDE 20 UNICORN should not be administered to breast-feeding women.

*Fertility*

Studies have shown that LEFLUNOMIDE 20 UNICORN has no effect on male and female fertility. 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 operate machinery

Patients should refrain from driving cars and using machinery in case of side effects such as dizziness which may impair the patient's ability to concentrate and to react properly.

## 4.8 Undesirable effects

| System organ class | Frequency | Undesirable effects |
|---|---|---|
| **Summary of the safety profile:** | *Frequent:* | Abdominal pain, anorexia, asthenia, CPK increased, diarrhoea, dizziness, dry skin, eczema, elevation of liver parameters (transaminases (especially ALT), less often gamma-GT, alkaline phosphatise, bilirubin)), headache, increased hair loss, leucopenia, mild allergic reactions, mild increase in blood pressure, nausea, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), paraesthesia, rash (including maculo-papular rash), pruritus, tenosynovitis, vomiting and weight loss (usually insignificant) |
| **Infections and infestations:** | *Less frequent:* | Severe infections, including sepsis which may be fatal<br>Leflunomide may increase susceptibility to infections, including opportunistic infections (see also section 4.4) like other medicines with immunosuppressive potential. Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia) |
| **Neoplasms, benign, malignant and unspecified (incl. cysts:** | *Frequency unknown:* | The use of some immunosuppressive medicines increases the risk of malignancy, particularly lymphoproliferative disorders |

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|---|---|---|
| **Blood and the lymphatic system disorders:** | *Frequent:*<br>*Less frequent:* | Leucopoenia (leucocytes >2 G/L)<br>Agranulocytosis, anaemia, eosinophilia, mild thrombocytopenia (platelets <100 G/L), pancytopenia (probably by antiproliferative mechanism)<br>Recent concomitant or consecutive use of potentially myelotoxic medicines may be associated with a higher risk of haematological effects |
| **Immune system disorders:** | *Frequent:*<br>*Less frequent:* | Mild allergic reactions<br>Severe anaphylactic/anaphylactoid reactions |
| **Metabolism and nutrition disorders:** | *Frequent:*<br>*Less frequent:*<br><br>*Frequency unknown:* | CPK increased<br>Hyperlipidaemia, hypokalaemia, hypophosphataemia, LDH increased<br>Hypouricaemia |
| **Psychiatric disorders:** | *Less frequent*: | Anxiety |
| **Nervous system disorders:** | *Frequent:*<br>*Less frequent:* | Headache, dizziness, paraesthesia<br>Peripheral neuropathy, taste disturbances |
| **Vascular disorders:** | *Frequent:*<br>*Less frequent*: | Mild increase in blood pressure<br>Severe increase in blood pressure |
| **Respiratory, thoracic and mediastinal disorders:** | *Less frequent*:<br><br>*Frequency unknown:* | Interstitial lung disease (including interstitial pneumonitis) which may be fatal<br>Pulmonary hypertension |
| **Gastrointestinal** | *Frequent:* | Abdominal pain, anorexia, collagenous colitis, |

| | | |
|---|---|---|
| **disorders:** | | colitis including microscopic colitis such as lymphocytic colitis, diarrhoea, nausea, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), vomiting |
| | *Less frequent*: | Pancreatitis, taste disturbances |
| **Hepato-biliary disorders:** | *Frequent:* | Elevation of liver parameters (e.g. transaminase, 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* | Dry skin, eczema, increased hair loss, pruritis, rash (including maculopapular rash) |
| | *Less frequent*: | Urticaria, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, vasculitis, necrotising vasculitis |
| | *Frequency unknown:* | Cutaneous lupus erythematosus, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), pustular psoriasis or worsening psoriasis |
| **Musculoskeletal and connective tissue disorders:** | *Frequent:* | Tenosynovitis |
| | *Less frequent*: | Tendon rupture |
| **Renal and urinary disorders:** | *Frequency unknown:* | Renal failure |
| **Reproductive system and breast disorders:** | *Less frequent*: | Marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility |

| | | |
|---|---|---|
| **General disorders and administration site conditions:** | *Frequent:* | Asthenia, weight loss (usually insignificant) |

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continues monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via "6.04 Adverse Drug Reactions Reporting Form", found under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Adverse reactions also must be reported to Unicorn Pharmaceuticals (Pty) Ltd to enquiries@unicornpharma.co.za

## 4.9 Overdose

**Signs and symptoms**

There have been reports of accidental overdose in patients taking LEFLUNOMIDE 20 UNICORN daily up to five times the recommended daily dose for several days and reports of acute overdose in adults and children. In the majority of case reports of overdose, no adverse events were reported. Consistent with the safety profile for leflunomide, adverse events were abdominal pain, anaemia, diarrhoea, elevated liver enzymes, leucopenia, nausea, pruritis and rash.

**Management of overdose**

In the event of relevant overdose or toxicity, cholestyramine or charcoal must be given 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, 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 Pharmacodynamics properties:

**Category and class:**

Pharmacological classification: A 3.1 Antirheumatoids (anti-inflammatory agents).

**Pharmacotherapeutic group:**

Selective immunosuppressants. ATC Code: L04AA13.

**Mode of action:** 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 □/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 31ml/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

Povidone K25

Crospovidone

Pregelatinized starch (corn)

Lactose monohydrate

Colloidal silicon dioxide

Magnesium Stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicine does not require any special storage conditions.

### 6.5 Nature and contents of container

Blister PVC 127 µm / PCTFE 51 µm / PVC 127 µm blister, sealed with an Aluminium 20 µm / PVDC 20 $gm^{-2}$sheet.

Leflunomide 20 Unicorn film coated tablets are supplied in packs of 30 tablets.

### 6.6 Special precautions for disposal and other handling

No special requirements

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town, 8001

South Africa

## 8 REGISTRATION NUMBER

56/3.1/0001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 14 November 2023

## 10 DATE OF REVISION OF THE TEXT

*Not applicable*