SUMMARY OF PRODUCT CHARACTERISTICS

Enclosed

SUMMARY OF PRODUCT CHARACTERISTICS

1. Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lefno-20 (Leflunomide Tablets USP 20 mg)
Each film-coated tablet contains:
Leflunomide USP….. 20mg

3. PHARMACEUTICAL FORM
Solid dosage form (Film Coated Tablet)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Leflunomide is indicated for the treatment of adult patients with:
• Active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
• Active psoriatic arthritis.
Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.
Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.

4.2 Posology and method of administration
Leflunomide tablets should be swallowed whole with sufficient amounts of liquid. It is administered orally as a single daily dose. The extent of leflunomide absorption is not affected if it is taken with food.
Loading dose
Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that leflunomide therapy be initiated with a loading dose of 100 mg per day for 3 days.
Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past.
Maintenance therapy
Daily dosing of 10 to 20 mg is recommended for treatment of patients with RA and 20 mg for treatment of psoriatic arthritis. A small cohort of patients, treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. Liver enzymes should be monitored and dose adjustments may be necessary. Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose

reduction and after stopping therapy with leflunomide, since it may take several weeks for metabolite levels to decline.
After stopping leflunomide treatment, an accelerated drug elimination procedure is recommended to reduce the plasma concentrations of the active metabolite, teriflunomide.
The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.
No routine dosage adjustment is required in patients above 65 years of age.
Hepatic impairment - Dedicated studies of the effect of hepatic impairment on leflunomide pharmacokinetics have not been conducted. Given the need to metabolize leflunomide into the active species, the role of the liver in drug elimination/recycling, and the possible risk of increased hepatic toxicity, the use of leflunomide in patients with hepatic impairment is not recommended.
Renal impairment - Dedicated studies of the effect of renal impairment on leflunomide pharmacokinetics have not been conducted. Given that the kidney plays an important role in drug elimination, caution should be used when leflunomide is administered to these patients. There is no dose adjustment recommended in patients with renal impairment.
Evaluation and testing prior to starting leflunomide: Prior to starting leflunomide treatment the following evaluations and tests are recommended:

- Evaluate patients for active tuberculosis and screen patients for latent tuberculosis infection
- Laboratory tests including serum alanine aminotransferase (ALT); and white blood cell, hemoglobin or hematocrit, and platelet counts
- For females of reproductive potential, pregnancy testing
- Check blood pressure

4.3 Contraindications
Combination of telmisartan and chlorthalidone tablets is contraindicated in patients with Leflunomide is contraindicated in patients with known hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to leflunomide, teriflunomide or any of the other components of leflunomide. Known reactions include anaphylaxis.
Leflunomide may cause fetal harm when administered to a pregnant woman. Leflunomide is contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception.
If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and begin a drug elimination procedure.

Leflunomide is also contraindicated in:

- 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.
- Patients with moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group.
- Breast-feeding women.

- Patients with severe hypoproteinemia e.g. in nephrotic syndrome.

- Patients with severe hepatic impairment.
- Patients being treated with teriflunomide

4.4 Special warnings and special precautions for use
WARNINGS

Embryo-fetal toxicity: Leflunomide may cause fetal harm when administered to a pregnant woman. Teratogenicity and embryo-lethality occurred in animal reproduction studies with leflunomide at doses lower than the human exposure level. Leflunomide is contraindicated for use in pregnant women. Exclude pregnancy before starting treatment with leflunomide in females of reproductive potential. Advise females of reproductive potential to use effective contraception during leflunomide treatment and during an accelerated drug elimination procedure after leflunomide treatment. If a woman becomes pregnant while taking leflunomide, stop treatment with leflunomide, apprise the patient of the potential risk to a fetus, and perform an accelerated drug elimination procedure to achieve non-detectable plasma concentrations of teriflunomide, the active metabolite of leflunomide. Upon discontinuing leflunomide, it is recommended that all females of reproductive potential undergo an accelerated drug elimination procedure. Women receiving leflunomide treatment who wish to become pregnant must discontinue leflunomide and undergo an accelerated drug elimination procedure, which includes verification that plasma concentrations of the active metabolite of leflunomide, teriflunomide, are less than 0.02 mg/L (0.02 mcg/mL). Based on animal data, human plasma concentrations of teriflunomide of less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal embryo-fetal risk

Immunosuppression, bone marrow suppression and risk of serious infections - Leflunomide is not recommended for patients with severe immunodeficiency (e.g. AIDS), bone marrow dysplasia, or severe, uncontrolled infections. In the event that a serious infection occurs, it may be necessary to interrupt therapy with leflunomide and initiating the accelerated drug elimination procedure. Medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections especially *Pneumocystis jiroveci* pneumonia, tuberculosis (including extra-pulmonary tuberculosis), and aspergillosis. Severe infections including sepsis, which may be fatal, have been reported in patients receiving leflunomide, especially *Pneumocystis jiroveci* pneumonia and aspergillosis. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection. Cases of tuberculosis were observed in clinical studies with teriflunomide, the metabolite of leflunomide. Before starting treatment, all patients should be evaluated for active and inactive (“latent”) tuberculosis, as per commonly used diagnostic tests. 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.

Leflunomide has not been studied in patients with a positive tuberculosis screen, and the safety of leflunomide in individuals with latent tuberculosis infection is unknown. Patients testing positive in tuberculosis screening should be treated by standard medical practice prior to therapy with leflunomide and monitored carefully during leflunomide treatment for possible reactivation of the infection.
There have been rare reports of pancytopenia, agranulocytosis and thrombocytopenia in patients receiving leflunomide alone. These events have been reported most frequently in patients, who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality.
Patients taking leflunomide should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6 to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking leflunomide, treatment with leflunomide should be stopped, and an accelerated drug elimination procedure should be performed to reduce the plasma concentration of leflunomide active metabolite, terflunomide.

In any situation in which the decision is made to switch from leflunomide to another anti-rheumatic agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Leflunomide washout with cholestyramine or charcoal may decrease this risk, but also may induce disease worsening if the patient had been responding to leflunomide treatment.
Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants.
Hepatotoxicity - Severe liver injury, including fatal liver failure, has been reported in patients treated with leflunomide. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) >2xULN before initiating treatment, are at increased risk and should not be treated with leflunomide. Concomitant use of leflunomide with other potentially hepatotoxic drugs may increase the risk of liver injury. Use caution when leflunomide is given with other potentially hepatotoxic drugs. Monitoring of ALT levels is recommended at least monthly for six months after starting leflunomide, and thereafter every 6-8 weeks. If ALT elevation > 3 fold ULN occurs, interrupt leflunomide therapy while investigating the probable cause of the ALT elevation by close observation and additional tests. If leflunomide-induced liver injury is suspected, stop leflunomide treatment, start an accelerated drug elimination procedure and monitor liver tests weekly until normalized. If leflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of leflunomide therapy may be considered. In addition, if leflunomide and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing.
Leflunomide treatment as monotherapy or in combination with methotrexate was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. 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. Most transaminase elevations were mild (<2-fold ULN) and usually resolved while continuing treatment. Marked elevations (>3-fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. It was notable that the absence of folate use was associated with a considerably greater incidence of liver enzyme elevation on methotrexate. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

Given the possible risk of increased hepatotoxicity, and the role of the liver in drug activation, elimination and recycling, the use of leflunomide is not recommended in patients with significant hepatic impairment or evidence of infection with hepatitis B or C viruses.

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). 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 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.

Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms - Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving leflunomide. If a patient taking leflunomide develops any of these conditions, leflunomide therapy should be stopped, and a drug elimination procedure is recommended. In such case, re-exposure to leflunomide is contraindicated. Putuslar 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.

Malignancy and lymphoproliferative disorders - The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression with leflunomide. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of leflunomide, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with leflunomide. In such cases re-exposure to leflunomide is contra-indicated. 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.

Peripheral Neuropathy- Cases of peripheral neuropathy have been reported in patients receiving Leflunomide. Most patients improved after discontinuation of Leflunomide, but some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking leflunomide develops a peripheral neuropathy, consider discontinuing leflunomide therapy and performing an accelerated drug elimination procedure.

Blood pressure monitoring – In studies with the active metabolite of leflunomide, teriflunomide, elevations in blood pressure were observed in some subjects. Blood pressure must be checked before the start of leflunomide treatment and periodically thereafter.

Use in women of childbearing potential – Leflunomide may cause fetal harm when administered during pregnancy. Advise females of the potential risk to the fetus. Advise females to notify their healthcare provider immediately if pregnancy occurs or is suspected during treatment. Women receiving leflunomide treatment who wish to become pregnant should discontinue leflunomide and undergo an accelerated drug elimination procedure to achieve plasma teriflunomide concentrations of less than 0.02 mg/L (0.02 mcg/mL). Exclude pregnancy in females of reproductive potential before starting treatment with leflunomide. Advise females of reproductive potential to use effective contraception during treatment with leflunomide and while undergoing a drug elimination procedure until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.

Procedure for accelerated elimination of leflunomide and its active metabolite – The active metabolite of leflunomide, teriflunomide, is eliminated slowly from the plasma. Use of an accelerated drug elimination procedure will rapidly reduce plasma concentrations of leflunomide and its active metabolite, teriflunomide. Therefore, an accelerated elimination procedure should be considered at any time after discontinuation of leflunomide, and in particular, when a patient has experienced a severe adverse reaction (e.g., hepatotoxicity, serious infection, bone marrow suppression, Steven Johnson Syndrome, toxic epidermal necrolysis, peripheral neuropathy, interstitial lung disease), suspected hypersensitivity, or has become pregnant. It is recommended that all women of childbearing potential undergo an accelerated elimination procedure after stopping leflunomide treatment. Without use of an accelerated drug elimination procedure, it may take up to 2 years to reach plasma teriflunomide concentrations of less than 0.02 mg/L, the plasma concentration not associated with embryo-fetal toxicity in animals.

Elimination can be accelerated by the following procedures:

Administer cholestyramine 8 grams 3 times daily for 11 days.

Alternatively, administer 50 grams of activated charcoal powder (made into a suspension) orally every 12 hours for 11 days.

Verify plasma teriflunomide concentrations of less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma teriflunomide concentrations are higher than 0.02 mg/L, repeat cholestyramine and/or activated charcoal treatment.

The duration of accelerated drug elimination treatment may be modified based on the clinical status and tolerability of the elimination procedure. The procedure may be repeated as needed, based on teriflunomide concentrations and clinical status. Use of the

accelerated drug elimination procedure may potentially result in return of disease activity if the patient had been responding to leflunomide treatment.

Interstitial lung disease - Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide and has been associated with fatal outcomes. The risk of leflunomide-associated interstitial lung disease is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely at any time during therapy and has a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation as appropriate. If discontinuation of the drug is necessary, consider performing an accelerated drug elimination procedure.

Renal insufficiency - Single dose studies in dialysis patients show a doubling of the free fraction of teriflunomide in plasma. There is no clinical experience in the use of leflunomide in patients with renal impairment. Caution should be used when administering this drug in this population.

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

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 teriflunomide plasma concentration is then measured for the first time. Thereafter, the teriflunomide 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.

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.

Laboratory tests

Due to a specific effect on the brush border of the renal proximal tubule, leflunomide has a uricosuric effect. A separate effect of hypophosphaturia is seen in some patients. These effects have not been seen together, nor have there been alterations in renal function.

Usage in paediatrics

The safety and effectiveness of leflunomide in paediatric patients with polyarticular course juvenile rheumatoid arthritis (JRA) have not been fully evaluated.

Usage in geriatrics

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is needed in patients over 65.

4.5 Interaction with other medicinal products and other forms of Interaction

Potent CYP and transporter inducers: Leflunomide is metabolized by CYP450 metabolizing enzymes. Concomitant use of leflunomide and rifampin, a potent inducer of CYP and transporters, increased the plasma concentration of teriflunomide by 40%. However, when co-administered with the metabolite, teriflunomide, rifampin did not affect its pharmacokinetics. No dosage adjustment is recommended for leflunomide when coadministered with rifampin. Because of the potential for leflunomide concentrations to continue to increase with multiple dosing, caution should be used if patients are to be receiving both leflunomide and rifampin

Cholestyramine and charcoal - Administration of cholestyramine or activated charcoal resulted in a rapid and significant decrease in plasma teriflunomide (the active metabolite of leflunomide) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of the active metabolite of leflunomide.

Hepatotoxic drugs - Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances. This is also to be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small combination study of leflunomide with methotrexate, a 2- to 3-fold elevation in liver enzymes was seen. However no pharmacokinetic interaction was observed between these two drugs.

CYP2C8 substrates - Teriflunomide is an inhibitor of CYP2C8 *in vivo*. In patients taking leflunomide, exposure of drugs metabolized by CYP2C8 (e.g., paclitaxel, pioglitazone, repaglinide, rosiglitazone) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required.

CYP1A2 substrates - Teriflunomide, the active metabolite of leflunomide, may be a weak inducer of CYP1A2 *in vivo*. In patients taking leflunomide, exposure of drugs metabolized by CYP1A2 (e.g., alosetron, duloxetine, theophylline, tizanidine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required.

NSAIDs - In *in vitro* studies, teriflunomide was shown to cause increases ranging from 13 - 50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown; however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide - In *in vitro* studies, teriflunomide was shown to cause increases ranging from 13 - 50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Warfarin and other coumarin anticoagulants– Co-administration of warfarin with leflunomide resulted in increase in prothrombin time. Coadministration of leflunomide with warfarin requires close monitoring of the international normalized ratio (INR) because teriflunomide, the active metabolite of leflunomide, may decrease peak INR by approximately 25%.

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

Oral contraceptives - Teriflunomide may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with leflunomide.
Organic anion transporter 3 (OAT3) substrates- Teriflunomide inhibits the activity of OAT3 *in vivo*. In patients taking leflunomide, exposure of drugs which are OAT3 substrates (e.g., cefaclor, cimetidine, ciprofloxacin, penicillin G, ketoprofen, furosemide, methotrexate, zidovudine) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) which are OAT3 substrates as required.
BCRP and organic anion transporting polypeptide B1 and B3 (OATP1B1/1B3) substrates- Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 *in vivo*. For a patient taking leflunomide, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-Co reductase inhibitors (e.g., atorvastatin, nateglinide, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking leflunomide.
Phenytoin - *In vitro* studies of drug metabolism indicate that teriflunomide inhibits CYP 450 2C9, which is responsible for the metabolism of phenytoin. The clinical significance of these findings with regard to phenytoin is unknown. Caution is advised when leflunomide is given together with phenytoin.
Methotrexate – During 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. 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.

4.6 Undesirable effects
The adverse events with following classification of expected frequencies were reported: 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.
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), eosinophilia *Very rare:* agranulocytosis Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects; *Not known:* neutropenia, leukocytosis.
Cardiac disorders - *Common:* mild increase in blood pressure, chest pain, palpitation, thrombophlebitis of the leg, varicose vein; *Rare:* severe increase in blood pressure
Eye disorders – *Common:* blurred vision, eye disorder, papilledema, retinal hemorrhage
Gastrointestinal disorders - *Common:* diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain, colitis including

microscopic colitis such as lymphocytic colitis, collagenous colitis,anorexia, bilirubinemia, flatulence, gamma-GT increased, salivary gland enlarged, sore throat, dry mouth ; *Uncommon:* taste disturbances; *Very rare:* pancreatitis

General disorders and administration site conditions - *Common:* anorexia, weight loss (usually insignificant), asthenia, back pain, malaise

Hepatobiliary disorders - *Common:* elevation of liver enzymes (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.

Immune system disorders - *Common:* mild allergic reactions; *Very rare*: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis; *Not known:* angioedema

Infections and infestations – *Common:* abscess, flue syndrome, vaginal monilasis; *Rare:* severe infections, including sepsis which may be fatal. Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections. Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia); *Not known:* Opportunistic infections

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

Musculoskeletal and connective tissue disorders - *Common:* tenosynovitis; joint disorder; *Uncommon:* tendon rupture

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

Nervous system disorders - *Common:* paraesthesia, headache, dizziness, somnolence; *Very rare:* peripheral neuropathy

Psychiatric disorders - *Uncommon:* anxiety

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

Respiratory, thoracic and mediastinal disorders – *Common:* dyspnea; *Rare:* interstitial lung disease (including interstitial pneumonitis and pulmonary fibrosis), which may be fatal; *Not known:* pulmonary hypertension, bronchitis, rhinitis

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, DRESS, vasculitis including cutaneous necrotizing vasculitis, alopecia

4.7. OVERDOSAGE

In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200 - 500 mg/kg and 100 mg/kg, respectively (approximately >350 times the maximum recommended human dose, respectively).

There have been reports of chronic overdose in patients taking leflunomide at daily dose up to five times the recommended daily dose and reports of acute overdose in adults or

children. The most frequent adverse events observed were diarrhea, abdominal pain, nausea, leukopenia, anemia, elevated liver function tests, pruritus and rash.
In the event of a significant overdose or toxicity, perform an accelerated drug elimination procedure to accelerate elimination.
Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that teriflunomide, the primary metabolite of leflunomide, is not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Leflunomide is a disease modifying anti-rheumatic agent.
It is an isoxazole immunomodulatory agent, which inhibits the human enzyme 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.

Pharmacokinetics

Following oral administration, leflunomide is metabolized to an active metabolite, teriflunomide, which is responsible for essentially all of leflunomide's *in vivo* activity. Plasma concentrations of the parent drug, leflunomide, have been occasionally seen at very low concentrations. Co-administration of leflunomide tablets with a high fat meal did not have a significant impact on teriflunomide plasma concentrations. Teriflunomide is extensively bound to plasma protein (>99%) and is mainly distributed in plasma. Teriflunomide, the active metabolite of leflunomide, has a median half-life of 18-19 days in healthy volunteers. Cytochrome P450 (CYP) 1A2, 2C19 and 3A4 are involved in leflunomide metabolism. In vivo, leflunomide is metabolized to one primary (teriflunomide) and many minor metabolites. Teriflunomide, the active metabolite of leflunomide, is eliminated by direct biliary excretion of unchanged drug as well as renal excretion of metabolites. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After an accelerated elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces). Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that teriflunomide is not dialyzable.

Special populations

Smoking - Smokers have a 38% increase in clearance over nonsmokers; however, no difference in clinical efficacy was seen between smokers and nonsmokers.

5.3 Preclinical safety data

---

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

- Lactose Monohydrate
- Dried Maize Starch
- Crospovidone (Kollidone CL)
- Povidone K-30
- Colloidal Silicon Dioxide

- Magnesium Stearate
- Opadry White 03F58750
- Isopropyl Alcohol

6.2 Incompatibilities
None

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Labelled container pack of 30 tablets along with leaflet.

6.6 Special precautions for disposal
None.

7. MARKETING AUTHORISATION HOLDER

Ipca Laboratories Ltd.
Regd. Office: 48, Kandivli Industrial Estate,
Mumbai 400 067, India