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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

# LEFRA

(Leflunomide tablets, 10 mg and 20 mg)

**COMPOSITION :**

**LEFRA 10 :** Each film coated tablets contains Leflunomide 10mg
**LEFRA 20 :** Each film coated tablets contains Leflunomide 20mg

**PROPERTIES :**

Leflunomide is an immunomodulatory agent, which inhibits dihydroorotate dehydrogenase (an enzyme involved in de- novo pyrimidine synthesis) and has antiproliferative activity.

**INDICATIONS :**

Leflunomide is a disease modifying anti rheumatic drug (DMARD) indicated in adults for the treatment of active Rheumatoid Arthritis (RA) to reduce signs and symptoms, and to retard structural damage as evidenced by X-ray erosions and joint space narrowing.

Aspirin, NSAIDS and/ or corticosteroids may be co-administered or continued with the treatment of LEFRA. The combined use of LEFRA with antimalarials, intramuscular gold injection, D penicillamine, azathioprine, has not been adequately studied.

**DOSAGE AND METHOD OF ADMINISTRATION :**

**LOADING DOSE**

Due to the long half-life of the drug, a loading dose is needed to provide a steady state concentration more rapidly. It is recommended that LEFRA therapy be initiated with a loading dose of one 100mg tablet per day for 3 days.

**MAINTENANCE THERAPY**

Daily dosing of 20mg is recommended for the treatment of patients with RA. Doses higher than 20mg/day are not recommended. If dosing at 20mg is not tolerated then the dose can be reduced to 10mg/day. Liver function tests should be carried out at regular intervals and dosage adjustment should be made accordingly if there are any abnormal elevations in the liver enzymes (>3 fold Upper Limit of Normal [ULN]). Due to the prolonged half-life of the active metabolite of Leflunomide, patients should be carefully observed after dose reduction, since it might take several weeks for metabolite levels to decline.

**Pediatric Use**

The safety and efficacy of Leflunomide in the pediatric population have not been studied. Use of Leflunomide in patients less than 18 years of age is not recommended.

**Geriatric Use**

No dosage adjustment is needed in patients over 65.

**CONTRAINDICATIONS AND WARNINGS :**

**Pregnancy must be excluded before the start of treatment with LEFRA. LEFRA is contraindicated in pregnant women, or women of child bearing potential who are not using reliable contraception. Pregnancy must be avoided during LEFRA treatment or prior to the completion of the drug elimination procedure after LEFRA treatment**

LEFRA is contraindicated in individuals who are hypersensitive to the drug and any other components of LEFRA.

**Immunosuppression Potential**

Leflunomide is not recommended in patients with immunodeficiency, those with bone marrow dysplasia, or those with serious infections or severe hypoprotienemia. Leflunomide should be administered with caution to patients who were on any other immunosuppressive drug with regular clinical and hematological monitoring. 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.

**Skin Reactions**

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving Leflunomide. If any severe drug related allergic reactions are reported it is recommended to discontinue the drug immediately and a drug elimination procedure is recommended.

**Hepatotoxicity**

Leflunomide treatment is reported to be associated with elevation of liver enzymes, primarily ALT and AST. In a significant number of patients these effects were generally reversible. Most transaminase elevations were mild (2-fold ULN) and usually resolved while continuing treatment. Marked elevations (>3-fold ULN) occurred infrequently and were reversed with dose reduction or discontinuation of therapy. ALT (SGPT) should be performed at baseline and monitored initially at monthly intervals then, if stable, at intervals determined by the individual clinical situation.

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations >2-fold ULN, dose reduction to 10 mg/day may allow continued administration of LEFRA. If elevations >2 but <3-fold ULN persist despite dose reduction, liver biopsy is recommended if continued treatment is desired. If elevations >3-fold ULN persist despite dose reduction, LEFRA should be discontinued and cholestyramine should be administered with close monitoring, including treatment with cholestyramine as indicated. Rare elevations of alkaline phosphatase and bilirubin have been observed.

**Pre-existing Hepatic Disease**

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.

**If situation warrants active drug elimination, the general drug elimination procedure is summarized as below :**

**To achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 µg/ml) after stopping treatment with LEFRA :**

**1) Administer cholestyramine 8 grams 3 times daily for 11 days. (The 11 days need not be consecutive unless there is a need to lower the plasma level rapidly.)**

**2) Verify plasma levels less than 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.**

**OR**

**3) Administer activated charcoal (powder made into a suspension) orally or via nasogastric tube, 50g every 6 hours for 24 hrs to reduce the plasma concentration of active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.**

**Without the drug elimination procedure, it may take up to 2 years for the plasma M1 metabolite levels to reach less than 0.02 mg/L, due to individual variation in drug clearance. These drug elimination procedures may be repeated if clinically necessary.**

**PRECAUTIONS :**

**General**

***Need for Drug Elimination***

The active metabolite of leflunomide is eliminated slowly from the plasma. In instances of any serious toxicity from Leflunomide, including hypersensitivity, use of a drug elimination procedure as described in this section is highly recommended to reduce the drug concentration more rapidly after stopping Leflunomide therapy. If hypersensitivity is the suspected clinical mechanism, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. The duration may be modified based on the clinical status of the patient.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of M1 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 M1, by 37% in 24 hours and by 48% in 48 hours. These drug elimination procedures may be repeated if clinically necessary.

***Renal Insufficiency***

Single dose studies in dialysis patients show a doubling of the free fraction of M1 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 Leflunomide should be considered when contemplating administration of a live vaccine after stopping Leflunomide.

***Respiratory Infections :***

Because of the immunosuppressive potential of LEFRA it is likely to cause respiratory infections. Any such developments should be immediately presented before the concerned Rheumatologist.

**DRUG INTERACTIONS :**

***Cholestyramine and Charcoal :***

Co-administration of Cholestyramine and charcoal will result in rapid and significant reductions in plasma M1 (the active metabolite of Leflunomide) concentration.

***Oral contraceptives and Cimetidine :***

There was lack of significant interaction between Leflunomide and tri-phasic oral contraceptives, and cimetidine.

***Methotrexate :***

Co-administration of Leflunomide with methotrexate has no pharmacokinetic interactions. However, co-administration increased the risk of hepatotoxicity.

***Rifampin :***

Following concomitant administration of a single dose of Leflunomide to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when Leflunomide was given alone. Because of the potential for Leflunomide levels to continue to increase with multiple dosing, caution should be used if patients are to receive both Leflunomide and rifampin.

**DRUG ABUSE AND DEPENDENCE**

LEFRA has no known potential for abuse or dependence.

**ADVERSE REACTIONS :**

The most common adverse events with Leflunomide are gastrointestinal symptoms (including diarrhoea, nausea and vomiting, abdominal pain and oral ulceration), allergic reactions (e.g. rash, pruritis and rarely anaphylaxis), alopecia and elevated liver enzyme levels. Anorexia, weight loss, headache, paraesthesia, hypertension and dizziness have also been reported. Infections may be more common. Rarely, severe haematological, hepatotoxic or allergic (e.g. severe skin reactions or anaphylaxis) reactions may occur. Patients should have LFTs, blood pressure and a full blood count taken before & during the treatment (after every 2 weeks for the first 6 months, then after every 8 weeks). If a serious reaction occurs, a washout procedure is recommended for rapid elimination of the drug from the body. The procedure for washout is described in above paragraphs.

**OVERDOSE :**

There is no human experience regarding Leflunomide overdosage. In the event of significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination.

**PHARMACOLOGICAL PROPERTIES :**

Leflunomide is an immunomodulatory agent belonging to a class of disease modifying anti rheumatic drug (DMARD), which is effective in the treatment of active Rheumatoid Arthritis. Leflunomide is metabolised in-vivo to its active metabolite M1, which arrests G1phase of the cell cycle of activated lymphocytes through its action on dihydroorotate dehydrogenase (DHODH), a key enzyme in the pathway of de-novo synthesis of rUMP. Since a roughly eightfold increase in levels of pyrimidine ribonucleotide synthesis is required for activated lymphocytes to complete their transition from G1phase of the cell cycle through S phase, an inhibition of de- novo pyrimidine ribonucleotides prevents clonal expansion of activated lymphocytes and leads to drug action as an immunomodulatory agent.

**PHARMACOKINETICS**

Leflunomide is converted to its active metabolite M1 in-vivo, which is responsible for all the pharmacological actions.

**Absorption**

The peak plasma levels of the metabolite are observed 6-12 hours after oral dosing of Leflunomide. Due to very long half life a loading dose of 100mg/day for 3 days is given for rapid attainment of steady state plasma levels. Without a loading dose it is estimated that it would require a minimum period of 2 months to achieve steady state plasma drug concentrations. Studies implied that the attainment of steady state plasma concentrations are following the loading dose and maintenance dose are dose proportional.

**Distribution**

Because of the extensive plasma protein binding (> 99.3) of the metabolite the volume of distribution (Vss=0.13 L/Kg) is very less.

**Metabolism**

Leflunomide is metabolised to a major metabolite M1 and many minor metabolites. One of its minor metabolite, 4-trifluoromethylaniline (TFMA) is quantifiable in plasma of some patients. Parent drug is rarely detectable in plasma. No specific site of metabolism is clearly known. The in-vitro and in-vivo studies suggest that liver and GI wall play an important role in the metabolism of Leflunomide. 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 drug metabolism.

**Elimination**

The active metabolite, M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion.

**EXPIRY DATE**

Do not use later than the date of expiry

**STORAGE**

Store below 30$^{o}$C
KEEP MEDICATIONS OUT OF REACH OF CHILDREN

**PRESENTATION**

**LEFRA 10**-It is available as Yellow coloured, round, biconvex film coated tablets In strips of 10 tablets.

**LEFRA 20**-It is available as Yellow coloured, round, biconvex film coated tablets with breakline on one side In strips of 10 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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