

NEW ZEALAND DATA SHEET

Leflunomide Sandoz[®]

Leflunomide Ph Eur film coated tablets 10 mg and 20 mg

Presentation

The product conforms to Leflunomide Tablets USP.

10 mg

Tablet, film coated, round, white, biconvex, plain one side and impressed 10 on the other. Each tablet contains leflunomide 10 mg.

20 mg

Tablet, film coated, round, light yellow, biconvex, plain both sides. Each tablet contains leflunomide 20 mg.

Actions

Leflunomide is a substituted phenylisoxazole carboxamide immunomodulatory agent that is effective in animal models of arthritis and other autoimmune diseases, allergy and transplantation.

Pharmacotherapeutic group

L04AA13 - Selective immunosuppressants, leflunomide.

Mechanism of action

Leflunomide is a prodrug that is rapidly metabolised *in vivo* to the active ring opened form, N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide also known as teriflunomide or A771726. It has immunomodulating/immunosuppressive characteristics, acts as an anti-proliferative agent, and displays weak anti-inflammatory properties. The anti-proliferative activity is reversed by the addition of uridine to the cell culture, indicating that A771726 acts at the level of the pyrimidine biosynthesis pathway. Leflunomide has demonstrated prophylactic and therapeutic effects in animal models of autoimmune disease. In animal models of chronic graft versus host disease and solid organ graft rejection, leflunomide has prolonged rejection time or reversed ongoing rejection reactions. In a model of experimental septicaemia, leflunomide did not alter the resistance of mice to bacterial pathogens.

Pharmacodynamic effects

Binding studies using radiolabelled ligand demonstrate that the active metabolite binds to and inhibits the human enzyme dihydroorotate dehydrogenase (DHODH), an enzyme involved in *de novo* pyrimidine synthesis. Together, these data suggest that, *in vivo*, at concentrations achievable in patients receiving leflunomide, pyrimidine synthesis in lymphocytes and other rapidly dividing cell populations may be inhibited. Further, the inhibition of tyrosine kinase activity has been reported, for both *in vitro* and *in vivo* situations. The *in vitro* activity does not seem to be mediated directly through enzyme inhibition and takes place only at much higher concentrations of A771726 than is necessary for the inhibition of DHODH.

Pharmacokinetics

Absorption

Following administration, leflunomide is rapidly and almost completely metabolised by the opening of the isoxazole ring to form the active metabolite, A771726, by first-pass metabolism in the gut wall and liver. Plasma samples taken 4 hours after the ingestion of leflunomide reveal only A771726. An

absolute bioavailability study has not been performed in man. In animals, however, the bioavailability of A771726 after administration of leflunomide ranged from 76% in dog to >90% in mouse. Following oral administration, peak levels of A771726 occurred between 6 to 12 hours after dosing. Due to the very long half-life of A771726 (about 2 weeks), a loading dose of 100 mg leflunomide for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly 2 months of dosing. There was evidence from multiple dosing studies in patients with rheumatoid arthritis that pharmacokinetic parameters were linear over the loading dose phase used in clinical trials (i.e., 100 mg daily for 3 days) and over daily maintenance doses of 5 to 25 mg. In these studies the clinical effect was closely related to plasma concentration of A771726 and to the daily dose of leflunomide. Factors such as age, sex and body size had only a small, clinically irrelevant influence on inter-individual variability in A771726 clearance. The following plasma concentrations following both loading doses and continued clinical dosing indicate that A771726 plasma levels are dose proportional.

A dosing study yielded the following pharmacokinetic parameters for A771726 after administration of leflunomide at maintenance doses of 5, 10, 25 mg/day for 24 days to patients (n = 54) with rheumatoid arthritis (mean \pm SD).

5 mg maintenance doses initiated by a 50 mg loading dose

- plasma concentration at 24 hours after loading dose 4.0 ± 0.6 mcg/ml
- plasma concentration at 24 hours after maintenance doses at steady state 8.8 ± 2.9 mcg/ml
- half life 15 ± 3 days

10 mg maintenance doses initiated by a 100 mg loading dose

- plasma concentration at 24 hours after loading dose 8.4 ± 2.1 mcg/ml
- plasma concentration at 24 hours after maintenance doses at steady state 18 ± 9.6 mcg/ml
- half life 14 ± 5 days

25 mg maintenance doses initiated by a 100 mg loading dose

- plasma concentration at 24 hours after loading dose 8.5 ± 2.2 mcg/ml
- plasma concentration at 24 hours after maintenance doses at steady state 63 ± 36 mcg/ml
- half life 18 ± 9 days

Relative to an oral solution, leflunomide tablets are 80% bioavailable. Food does not affect the bioavailability of leflunomide.

Distribution

In human plasma from healthy volunteers, A771726 was extensively bound (>99.3%) to albumin. The unbound fraction of A771726 was 0.62%. Binding of A771726 was linear up to 573 mcg/ml. Binding of A771726 appeared slightly reduced and more variable in plasma from patients with rheumatoid arthritis or chronic renal insufficiency such that the unbound fraction increased to 0.80% and 1.44% in these two patient groups, respectively. Consistent with extensive protein binding, A771726 had a low apparent volume of distribution (approximately 11 l). Average plasma concentration of A771726 at steady state is approximately 30 mcg/ml for a maintenance dose of 20 mg/day.

Biotransformation

Leflunomide is metabolised to one primary (A771726) and many minor metabolites. The metabolic biotransformation of A771726 is not controlled by a single enzyme and has been shown to occur in microsomal and cytosolic cellular fractions. At the present time the specific site of leflunomide metabolism is unknown. *In vivo* and *in vitro* studies suggest a role for both the gastro-intestinal wall and the liver in metabolism. In a study with carbon-14 radiolabelled leflunomide in three healthy men, no unchanged leflunomide was detected in plasma, urine or faeces. The only radiolabelled metabolite detected in plasma was A771726 and there was no preferential uptake by erythrocytes. The metabolite 4-trifluoromethylaniline has been detected in the plasma of animals and man but at concentrations about a thousand times lower than those measured for A771726 and often below the limit of quantification. Human concentrations were typically <10 ng/ml whilst the highest recorded values were approximately 20 ng/ml.

Elimination

The active metabolite, A771726, is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. In a study of radiolabelled leflunomide, excretion of radioactivity was slow, and between 89% and 94% of total radioactivity was excreted within 28 days. Approximately 43% of the total radioactivity was eliminated in the urine and 48% was eliminated in the faeces. The principal urinary metabolites were glucuronide products derived from leflunomide (mainly in 0 to 24 hour samples) and an oxanilic acid derivative of A771726. The principal faecal component was A771726. In small studies using activated charcoal (n = 1) or cholestyramine (n = 3) to facilitate drug elimination, the *in vivo* plasma half-life of A771726 was reduced from >1 week to approximately 1 day (refer to Overdosage). 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 A771726. Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that A771726 is not dialysable. After independent intravenous administration of A771726, clearance averaged 31 ml/hr with an elimination half-life of 10 days. A similar clearance estimate (29 ± 17 ml/hr) was obtained from population pharmacokinetics analysis of rheumatoid arthritis patients enrolled in pivotal safety and efficacy studies.

Special populations

Sex

The *in vivo* pharmacokinetics of leflunomide and A771726 have not been shown to vary consistently between male and female subjects.

Age

Age has been shown to cause a change in the *in vivo* pharmacokinetics of leflunomide and A771726 for children aged from 3 to 17 years. Data in patients older than 65 years are limited.

Smoking

A population based pharmacokinetic analysis of the Phase III data indicated that smokers had a 38% increase in clearance over non-smokers. However, no difference in clinical efficacy was seen between smokers and non-smokers.

Chronic renal impairment

In single-dose studies in patients (n = 6) with chronic renal impairment requiring either CAPD or haemodialysis, neither had a significant impact on circulating levels of A771726. The free fraction of A771726 was almost doubled, but the mechanism of this increase is not known. Given that the kidneys play a role in drug elimination, and without adequate studies of leflunomide use in patients with renal impairment, caution should be used when leflunomide is administered to these patients.

Hepatic impairment

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, and given the risk of hepatotoxicity, leflunomide is contraindicated in patients with impairment of liver function.

Indications

Rheumatoid arthritis, treatment of, to improve signs and symptoms, to retard joint destruction and to improve functional ability and quality of life. Leflunomide may be used in patients who have failed to respond to other treatments or as a first line of treatment in patients who have a contraindication to other treatments.

Active psoriatic arthritis, treatment of. Leflunomide is not indicated for the treatment of psoriasis that is not associated with manifestations of arthritic disease.

Dosage and administration

Dosage

Rheumatoid arthritis and psoriatic arthritis in adults

Loading dose

Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. Avoiding a loading dose may decrease the risk of adverse events if leflunomide is used in combination with methotrexate. This could be especially important for patients at increased risk of haematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past. (refer to the sections titled Concomitant use with hepatotoxic and haematotoxic agents and Hepatotoxicity in Warnings and precautions).

Maintenance dose

The recommended maintenance dose for rheumatoid arthritis is leflunomide 20 mg once daily. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated, the dose may be decreased to 10 mg daily. The recommended maintenance dose for psoriatic arthritis is 20 mg once daily.

Liver enzymes and haematological parameters must be monitored and dose adjustments or discontinuation may be necessary (refer to Warnings and precautions). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction since it may take several weeks for metabolite levels to decline.

An improvement in the patient's rheumatoid condition may begin as early as 4 weeks after starting therapy with leflunomide however there may be further improvement in the condition after 4 to 6 months of treatment.

At present there is not enough experience available to make dosage recommendations for patients with a serum creatinine concentration of >133 micromoles/l (1.5 mg/dl).

No dosage adjustment is required in the elderly.

Compatibility with other antirheumatic drugs

If the patient is already receiving NSAIDs and/or low dose corticosteroids, these may be continued after starting leflunomide.

Please refer to Interactions for information about co-administration with methotrexate and other hepatotoxic and haematotoxic drugs.

Rheumatoid arthritis and psoriatic arthritis in children

The safety and effectiveness of leflunomide in paediatric patients have not been fully evaluated. Leflunomide is not recommended for use in patients under 18 years.

Administration

Leflunomide Sandoz tablets should be swallowed whole with sufficient liquid. Absorption of leflunomide is not affected if it is taken with food.

Contraindications

Hypersensitivity to leflunomide or to any of the excipients in the tablets.

Severe immunodeficiency states, e.g. AIDS.

Significantly impaired bone marrow function or significant anaemia, leukopenia or thrombocytopenia due to causes other than rheumatoid arthritis.

Severe, uncontrolled infections.

Impaired liver function.

Pregnancy.

Women of childbearing potential who are not using reliable contraception during treatment with leflunomide and for a certain period of time thereafter, as long as the plasma levels of the active metabolite are above 0.02 mg/l, unless undergoing washout treatment (refer to the section titled Pregnancy and lactation in Warnings and precautions).

Breast feeding.

Severe hypoproteinaemia.

Current or former presentation of Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme.

Warnings and precautions

Warnings

Concomitant use with hepatotoxic and haematotoxic agents

Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic or haematotoxic drugs or when leflunomide treatment is followed by such drugs without a washout period. The possibility of additive risks of side effects may persist for a long time after switching treatments. Therefore, the initiation of leflunomide treatment has to be carefully considered given these benefit/risk aspects.

Increased monitoring frequency is advised when leflunomide is used in combination with other hepatotoxic and haematotoxic agents (refer to Interactions). Pancytopenia is a rare event, which has been reported with leflunomide, with a fatal outcome in isolated cases. These events have been reported most frequently in cases of recent, concomitant or subsequent use of potentially myelotoxic/haematotoxic agents, such as methotrexate (the incidence of pancytopenia associated with methotrexate alone is reported in published literature to be between 0.6% to 2.1%). If the patient presents any evidence of pancytopenia on routine haematological monitoring, stop leflunomide, commence the recommended washout procedure and continue close haematological monitoring until resolution is confirmed (refer to Overdosage). Concomitant treatment with methotrexate and/or other hepatotoxic medications is also associated with an increased risk of serious hepatic reactions.

Hepatotoxicity

In clinical trials, leflunomide treatment was associated with elevations of liver function tests, primarily ALT (SGPT) and AST (SGOT). These effects were generally reversible. Most transaminase elevations were mild (2 x ULN or less) and usually resolved while continuing treatment. Clinically significant elevations (between 2 and 3 x ULN) were less common and were generally asymptomatic and reversible with dose reduction or, if persistent, discontinuation of leflunomide. More marked elevations (>3 x ULN) occurred rarely and usually reversed with dose reduction; persistent elevations resolved after discontinuation of leflunomide. Overall, persistent elevations after dose reduction were uncommon and were usually associated with concomitant NSAID use. Biopsy data did not suggest that leflunomide was associated with the development of cirrhosis or hepatic fibrosis. Very rare cases of severe liver injury, with fatal outcome in isolated cases, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Although confounding factors were present in many cases, a causal relationship to leflunomide cannot be excluded. It is considered essential that monitoring recommendations are strictly adhered to (refer to Liver function monitoring).

In a combination clinical study of leflunomide in patients with persistent active rheumatoid arthritis receiving stable background methotrexate for at least 6 months without liver enzyme elevation (n = 263), 226 patients were co-administered leflunomide with methotrexate for up to 48 weeks. In this study, patients with inadequate response to a stable dose of methotrexate for 6 months, were administered leflunomide with a loading dose of 100 mg daily for 2 days and thereafter, patients received a maintenance dose of 10 mg daily. These doses are both lower than the recommended initial dose of monotherapy with leflunomide. If dosing at 10 mg/day was not well tolerated clinically,

the dose was decreased to 10 mg of leflunomide every other day. If the 10 mg daily dose was tolerated, but disease activity persisted at 8 weeks or thereafter, the dose of leflunomide was increased to a maximum of 20 mg daily. In the 6 month placebo-controlled study phase, the incidence of ALT elevations >3-fold ULN on leflunomide co-administered with methotrexate was 3.8% versus 0.8% when placebo was co-administered with methotrexate. The incidence of >3-fold ULN ALT elevations for leflunomide monotherapy in this and two other studies was 1.5% to 4.4%. ALT elevations 2-fold or less the ULN reversed to 2-fold or less the ULN and normalised to <1.2-fold ULN with leflunomide dose reduction or discontinuation. Milder elevations between 1.2 and <2-fold ULN normalised without change in leflunomide dose in most cases, although a minority normalised after dose reduction or discontinuation.

Respiratory

Interstitial lung disease has been reported rarely during treatment with leflunomide (refer to Adverse effects). Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, with or without fever may be a reason for further investigation. Discontinuation of the therapy and implementation of a wash out with cholestyramine (see overdose) may be appropriate. Patients should be informed about the early warning signs of interstitial lung disease and asked to contact their physician as soon as possible if these symptoms appear or worsen during therapy.

Interstitial lung disease presenting acutely (interstitial pneumonitis) may occur more frequently with concomitant methotrexate.

Immunosuppression

Although there is no clinical experience in the following patient populations, leflunomide is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe uncontrolled infections because of the theoretical potential for immunosuppression.

In the event that a serious infection occurs, it may be necessary to interrupt therapy with leflunomide and administer cholestyramine or charcoal (refer to Overdosage). Rarely, severe infections including sepsis, which may be fatal, have been reported in patients receiving leflunomide. 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.

In post-marketing experience, there have been reports of pancytopenia (rare), agranulocytosis (very rare) and thrombocytopenia (rare) in patients receiving leflunomide (refer to Concomitant use with hepatotoxic and haematotoxic agents including methotrexate). In most of these cases, patients received concomitant treatment with methotrexate or other immunosuppressive agents or they had recently discontinued these therapies. Some cases had a prior history of significant haematologic abnormality. If leflunomide is used in such patients, it should be done with caution and with frequent haematologic monitoring (refer to Haematological monitoring). The use of leflunomide in combination therapy with methotrexate has not been adequately studied in a controlled setting.

If evidence of bone marrow suppression occurs in a patient taking leflunomide, treatment with leflunomide should be stopped and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide (refer to Overdosage).

In any situation in which the decision is made to switch from leflunomide to another anti-rheumatic agent with a known potential for haematologic suppression, it would be prudent to monitor for haematologic 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.

In dogs treated with leflunomide, a delayed healing of accidental cornea lesions was observed. This effect may be attributed to the immunosuppressive effect of leflunomide. Its clinical relevance is, however, unclear.

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

Skin reactions

In case of ulcerative stomatitis, leflunomide administration should be discontinued. Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with leflunomide. When potentially severe skin and/or mucosal reactions are observed, leflunomide and any other possibly associated medication must be discontinued. Cholestyramine or charcoal should be used immediately to reduce the plasma concentration of leflunomide (refer to [Overdosage](#)). In such cases, a complete washout is essential and re-exposure to leflunomide is contra-indicated.

Washout Procedure for severe Adverse Reactions

In light of the long half-life of teriflunomide [A771726] (typically 1 to 4 weeks), adverse reactions may eventuate or remain even after administration of leflunomide has ceased (see [Adverse effects](#)). In the event of a severe adverse reaction to leflunomide, or if teriflunomide [A771726] needs to be cleared from the body quickly, then cholestyramine or charcoal has to be initiated as described in the [Overdosage](#) section and continued or repeated as necessary. In the case of suspected severe immunological/allergic reactions, prolonged cholestyramine or charcoal administration may be needed to achieve rapid and sufficient clearance.

Washout procedures need to be performed when serious effects occur (for example hepatotoxicity, haematotoxicity or allergic reactions), in the case of desired or unintended pregnancy and if for any other reason teriflunomide [A771726] needs to be cleared from the body quickly.

Precautions

Patients with renal impairment

Leflunomide was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of A771726 in CAPD subjects appeared to be similar to those of healthy volunteers. A more rapid elimination of A771726 was observed in haemodialysis subjects which was not due to extraction of drug in the dialysate but instead to displacement of protein binding. Caution should be used when leflunomide is administered to patients with renal impairment (refer to [Special populations](#)).

Infections

It is known that medications with immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections, and these may be more severe in nature. Infections may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to stop leflunomide and administer a washout with cholestyramine (refer to [Overdosage](#)).

Use in males

Available information does not suggest that leflunomide would be associated with an increased 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 leflunomide treatment and taking cholestyramine 8 g 3 times daily for 11 days or 50 g activated charcoal 4 times daily for 11 days.

Paediatric use

The safety and effectiveness of leflunomide in paediatric patients have not been fully evaluated. Leflunomide is not recommended for use in patients under 18 years.

Use in the elderly

Leflunomide should be used with caution in patients aged over 75 years as its safety and efficacy have not been studied in this age group.

Pregnancy and lactation

Use in pregnancy

Assigned Category X by the Australian Drug Evaluation Committee. This category includes medicines

which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

As A771726 is teratogenic in rats and rabbits; it may cause foetal harm in humans. Leflunomide must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and for a certain period of time thereafter, being the waiting period or abbreviated wash-out period described below. Pregnancy must be excluded before starting treatment with leflunomide.

It is recommended that women of childbearing potential only receive leflunomide after it has been confirmed that they are using a reliable form of contraception. In a study in which leflunomide was given to healthy female volunteers concomitantly with a triphasic oral contraceptive containing 30 mcg ethinylestradiol, there was no reduction in contraceptive activity and A771726 pharmacokinetics were within predicted ranges.

Patients must be advised that if there is any delay in the onset of menses or any other reason to suspect pregnancy, they must notify their physician immediately to test for pregnancy. If the test is positive, the physician and patient must discuss the risk to the foetus. It is possible that by rapidly lowering the blood level of the active metabolite at the first delay of menses, using the drug elimination procedure described below, the risk to the foetus may be decreased.

Wash-out procedure

For women who have been treated with leflunomide and who may become pregnant, one of the following wash-out procedures is recommended prior to conception after stopping treatment with leflunomide: cholestyramine 8 g is administered 3 times daily for a cumulative period of 11 days; alternatively, 50 g of activated charcoal is administered 4 times daily for a total period of 11 days. The 11 days do not need to be consecutive unless there is a need to lower the A771726 plasma level rapidly. Both cholestyramine and activated charcoal may influence the absorption of estrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with cholestyramine and activated charcoal. Use of alternative contraceptive methods is recommended.

Plasma monitoring

After the wash-out procedure has been performed, A771726 plasma levels <0.02 mg/l must be verified by 2 separate tests at least 14 days apart. Human plasma levels of the active metabolite <0.02 mg/l are expected to have minimal risk based on available data. Without the drug elimination procedure, it may take up to 2 years to attain A771726 levels <0.02 mg/l after discontinuing leflunomide treatment, due to individual variation in drug clearance. However, verification of A771726 levels <0.02 mg/l by 2 separate tests at an interval of at least 14 days is required.

Use in lactation

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Therefore women must not breast feed while they are receiving leflunomide.

Effects on ability to drive and use machines

This medicine is likely to produce minor or moderate adverse effects.

Other

Monitoring

To minimise the risk of serious adverse reactions, it is essential that all monitoring recommendations are strictly adhered to. Due to the prolonged half-life of A771726 (usually 1 to 4 weeks), adverse reactions may occur or persist even after leflunomide administration has been discontinued (refer to [Adverse effects](#)). If a severe adverse reaction to leflunomide occurs, or if for any reason A771726 needs to be cleared rapidly from the body, cholestyramine or charcoal has to be initiated as described in the [Overdosage](#) section and continued or repeated as clinically necessary. For suspected severe immunological/allergic reactions, more prolonged cholestyramine or charcoal administration may be

necessary to achieve rapid and sufficient clearance.

Washout procedures must be performed in circumstances when serious effects occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions), in the case of desired or unintended pregnancy and if for any other reason A771726 needs to be cleared rapidly from the body.

Haematological monitoring

A complete blood cell count, including differential white blood cell count and platelets, should be performed in all patients before the start of leflunomide treatment, and monthly for the first 6 months, followed by 6 to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressives, chronic monitoring should be monthly.

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 for incidence of haematological reactions is increased.

Liver function monitoring

ALT and AST must be checked before the start of leflunomide treatment and monitored at monthly or more frequent intervals for at least the first 6 months and then, if stable, every 6 to 8 weeks thereafter. In addition, if leflunomide and methotrexate are given concomitantly, ALT, AST and serum albumin testing must be performed monthly. For confirmed ALT or AST elevations between 2- and 3-fold the ULN, dose reduction may allow continued administration of leflunomide under close monitoring. For minor elevations in ALT or AST (<2-fold ULN), repeat testing in 2 to 4 weeks. For moderate elevations in ALT or AST between 2-fold and 3-fold the ULN, closely monitor, with LFTs every 2 to 4 weeks and dosage reduction. If ALT or AST elevations between 2- and 3-fold ULN persist or if ALT or AST elevations of more than 3-fold ULN are present, leflunomide should be discontinued. Cholestyramine or activated charcoal should be administered to more rapidly lower A771726 levels, with close monitoring including retreatment with cholestyramine or activated charcoal as indicated.

Blood pressure monitoring

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

Preclinical safety data

Antigenicity

Leflunomide was not antigenic in the active systemic and passive cutaneous anaphylaxis test in guinea pigs and was devoid of sensitising properties.

Mutagenicity

Leflunomide as A771726 was not mutagenic in the bacteria *Salmonella typhimurium* and *Escherichia coli* or Chinese hamster ovary cells, did not cause chromosomal damage in mouse and Chinese hamster bone marrow cells *in vivo*, and did not induce unscheduled synthesis of DNA in mammalian cells *in vitro*. A minor metabolite of leflunomide, trifluoromethylaniline, was mutagenic and caused chromosomal damage *in vitro*, but it did not cause chromosomal damage in Chinese hamster bone marrow cells *in vivo* at concentrations higher than those expected in humans.

Carcinogenicity

A two year carcinogenicity study of oral leflunomide in mice showed an increased incidence of malignant lymphoma in males given leflunomide 15 mg/kg/day, yielding plasma A771726 concentrations (AUC) similar to those expected in humans, an increase in bronchioalveolar adenomas in males given 5 mg/kg/day or more, yielding plasma A771726 concentrations (AUC) similar to or about 50% lower than that expected in humans, and an increase in bronchioalveolar adenomas and carcinomas in females given 1.5 mg/kg/day, yielding plasma A771726 concentrations (AUC) at least 10 to 20 times lower than that expected in humans. The increase in the development of malignant lymphomas was probably due to the immunosuppressant effect of leflunomide. A no-effect dose or AUC for the development of lung tumours in female mice was not established, but the relevance of these findings for humans was not clear. Leflunomide showed no carcinogenicity activity in rats given oral leflunomide at doses up to 6 mg/kg/day yielding plasma A771726 concentrations

(AUC) 25 to 65 times lower than that expected in humans.

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.

Impairment of fertility

Oral administration of leflunomide at doses up to 4 mg/kg/day, yielding plasma A771726 concentrations (AUC) about 10 to 25 times lower than that expected in humans, in rats had no effect on fertility. However, impairment of spermatogenesis has been observed in rats, dogs and mice treated with oral leflunomide at higher doses or for longer periods yielding plasma A771726 concentrations (AUC) similar to or much lower than that expected in humans.

Adverse effects

Clinical trials

Incidence 3% or more in any leflunomide treated group

The following adverse events were reported, regardless of causality, from controlled and uncontrolled clinical trials with leflunomide given to rheumatoid arthritis patients where in any trial, the incidence of the event in the leflunomide treated arm was 3% or more. Incidence rates reported here represent the aggregate population of all patients participating in these trials (n = 1339) that received leflunomide

Body as a whole

Allergic reaction 2%; asthenia 3%; flu syndrome 2%; infection 4%; injury accident 5%; pain 2%; abdominal pain 6%; back pain 5%.

Cardiovascular

Hypertension 10%; however, hypertension as a pre-existing condition was over-represented in all leflunomide treated groups in Phase III clinical trials. Analysis of new onset hypertension revealed no difference among the treatment groups. Chest pain 2%.

Gastrointestinal

Anorexia 3%; diarrhoea 17%; dyspepsia 5%; gastroenteritis 3%; abnormal liver enzymes 5%; nausea 9%; gastrointestinal/abdominal pain 5%; mouth ulcer 3%; vomiting 3%.

Metabolic and nutritional

Hypokalaemia 1%; weight loss 4%.

Musculoskeletal system

Arthralgia 1%; leg cramps 1%; joint disorder 4%; synovitis 2%; tenosynovitis 3%.

Nervous system

Dizziness 4%; headache 7%; paraesthesia 2%.

Respiratory system

Bronchitis 7%; increased cough 3%; respiratory infection 15%; pharyngitis 3%; pneumonia 2%; rhinitis 2%; sinusitis 2%.

Skin and appendages

Hair loss 10%; eczema 2%; pruritis 4%; rash 10%; dry skin 2%.

Urogenital system

Urinary tract infection 5%.

Differences between leflunomide and placebo were observed for diarrhoea, elevated liver enzymes (ALT and AST), hair loss and rash.

Incidence of 1 to 3% in any leflunomide treated group

The following adverse events were reported from controlled clinical trials with leflunomide given to rheumatoid arthritis patients where in any trial, the incidence of the event in the leflunomide treated arm ranged from 1 to 3%.

Body as a whole

Abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain.

Cardiovascular

Angina pectoris, migraine, palpitation, arrhythmia, tachycardia, vasculitis, vasodilation, varicose vein.

Gastrointestinal

Cholelithiasis, colitis, constipation, oesophagitis, flatulence, gastritis, gingivitis, melaena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder.

Endocrine

Diabetes mellitus, hyperthyroidism.

Haemic and lymphatic system

Anaemia (including iron deficiency anaemia), ecchymosis, leukopenia, lymphadenopathy.

Metabolic and nutritional

Increased creatine phosphokinase, peripheral oedema, hyperglycaemia, hyperlipidaemia.

Musculoskeletal system

Arthrosis, bursitis, muscle cramps, myalgia, bone necrosis, bone pain, tendon rupture.

Nervous system

Anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweat, vertigo.

Respiratory system

Asthma, dyspnoea, epistaxis, lung disorder.

Skin and appendages

Acne, contact dermatitis, fungal dermatitis, hair discoloration, haematoma, herpes simplex, herpes zoster, nail disorder, skin nodule, subcutaneous nodule, maculopapular rash, skin disorder, skin discoloration, ulcerated skin.

Special senses

Blurred vision, cataract, conjunctivitis, eye disorder, taste perversion.

Urogenital system

Albuminuria, cystitis, dysuria, haematuria, menstrual disorder, vaginal moniliasis, prostate disorder, urinary frequency.

Other less common adverse events seen in clinical trials include: one case of anaphylactic reaction occurring in Phase II following drug rechallenge after withdrawal due to rash (rare); urticaria, transient thrombocytopenia (uncommon), eosinophilia (rare); and leukopenia with a leukocyte count <2 G/l (rare). A causal relationship of these events to leflunomide has not been established.

Mild hyperlipidaemia may occur. Uric acid levels usually decrease due to a uricosuric effect. Laboratory findings for which a clinical relevance could not be established include small increases in LDH and CK, and a small decrease in phosphate.

The overall incidence of infections in clinical studies was comparable between patients taking leflunomide and those taking placebo. Immunosuppressive medications are, however, known to increase susceptibility to infections (refer to Warnings and precautions). In clinical studies, the incidence of rhinitis and bronchitis (5% vs. 2%) and pneumonia (3% vs. 0%) was slightly increased in patients treated with leflunomide compared to placebo. The overall incidence of infections was comparable between leflunomide and placebo. The risk of malignancy, particularly lymphoproliferative disorders, is also known to be increased with use of some immunosuppressive drugs.

When significant side-effects occur, the dosage of leflunomide may be reduced or treatment discontinued.

Post-marketing surveillance

The following adverse events reported during the post-marketing period are categorised by incidence.

Common - between 1 in 100 and 1 in 10

Mild allergic reactions (including maculopapular and other rashes), pruritus, eczema, dry skin, increased hair loss; increase in blood pressure; headache, dizziness, paraesthesia; weight loss; asthenia.

Uncommon - between 1 in 1000 and 1 in 100

Urticaria; thrombocytopenia with a platelet count <100G/l; taste disturbances, anxiety;

Rare - between 1 in 10,000 and 1 in 1000

Hepatitis, jaundice/cholestatic; interstitial lung disease (including interstitial pneumonitis), which may be fatal.

Eosinophilia, leukopenia with a leukocyte count <2 G/l, pancytopenia - however in most reported cases of pancytopenia, SJS and TEN, co-medication was given which is associated with the risk of pancytopenia or SJS or TEN. Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological side effects.

Severe infections, including opportunistic infections, and sepsis, which may be fatal. Most of the case reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, in addition to rheumatoid disease, which may predispose patients to infection.

Very rare < 1 in 10,000

Agranulocytosis; pancreatitis; peripheral neuropathy.

Very rare cases of severe liver injury such as hepatic failure and acute hepatic necrosis with fatal outcome in isolated cases, have been reported during treatment with leflunomide. This risk may be increased when leflunomide is combined with other DMARDs. Most of the cases occurred within the first 6 months of treatment. Although confounding factors were present in many cases, a causal relationship to leflunomide cannot be excluded. It is considered essential that monitoring recommendations are strictly adhered to.

Severe anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme. In case reports received so far, leflunomide treatment causality could not be established, but cannot be excluded.

Vasculitis, including cutaneous necrotising vasculitis. Due to the underlying disease, causality could not be established.

Interactions

Medicines and other pharmacologically active substances

The enzymes involved in the metabolism of leflunomide and its metabolites are not precisely known. *In vitro* studies indicate that A771726 inhibits cytochrome P450C9 (CYP2C9) activity. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide. The extensive protein binding of A771726 could lead to displacement of other highly-bound drugs.

Cimetidine

An *in vivo* interaction study with cimetidine, a non-specific cytochrome P450 inhibitor, has demonstrated a lack of a significant interaction.

Rifampicin

Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin, a non-specific cytochrome P450 inducer, A771726 peak levels were increased by approximately 40%, whereas the AUC was not significantly changed. The mechanism of this effect is unclear. Given the potential for A771726 levels to continually increase with multiple dosing, caution is advised if patients are to be receiving both leflunomide and rifampicin.

Warfarin

Increased prothrombin time when leflunomide and warfarin were co-administered has been rarely reported. *In vitro* plasma protein binding interaction studies with warfarin at clinically relevant concentrations showed no interaction. This does not exclude the possibility of an interaction by other means, such as inhibition of drug metabolism. This has not been studied.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (including COX-2 inhibitors) are known to cause hepatotoxicity, therefore caution is advised when leflunomide is used concomitantly (refer to [Warnings and precautions](#)). Studies showed that ibuprofen and diclofenac did not displace A771726 but were displaced by A771726 and the unbound fraction of these drugs was increased by 10 to 50%. In clinical trials, no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered.

Tolbutamide

A771726 was shown *in vitro* to increase the free fraction of tolbutamide to clinically relevant levels ranging from 13% to 50%. The clinical significance of this finding is unknown. Conversely, the unbound fraction of A771726 was increased 2 to 3 fold in the presence of tolbutamide.

Methotrexate

In a small (n = 30) combination study of patients receiving leflunomide 10 to 20 mg/day with methotrexate 10 to 25 mg/week, co-administration increased the risk of hepatotoxicity. Baseline disease characteristics reflect a patient population with active rheumatoid arthritis, defined as an average tender and swollen joint count of 16, and longstanding disease with mean duration of 13.6 years. No pharmacokinetic interaction was identified. A greater than 3-fold increase in liver enzymes was seen in five patients. All of these increases resolved, two with continuation of both drugs and three after discontinuation of leflunomide. A 2- to 3-fold increase was seen in an additional 5 patients. All elevations resolved, two with continuation of both drugs and three after discontinuation of leflunomide. Three patients met the following ACR criteria for liver biopsy: 1 Roegnik Grade I; 2 Roegnik Grade IIIa (refer to [Warnings and precautions](#)).

There is evidence from spontaneous reporting and prescribing data that interstitial pneumonitis may occur more frequently with concomitant methotrexate.

Hepatotoxic and haematotoxic drugs

Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic or haematotoxic drugs or when leflunomide treatment is followed by such drugs without a washout

period. The possibility of additive risks of side effects may persist for a long time after switching treatments. Therefore, the initiation of leflunomide treatment has to be carefully considered given these benefit/risk aspects.

Oral contraceptives

When leflunomide was administered concomitantly with a low-dose oral contraceptive to healthy female volunteers, there was no effect on either the anti-ovulatory activity of the contraceptive or the pharmacokinetics of A771726.

Vaccinations

No clinical data are available concerning the efficacy and safety of vaccinations under leflunomide treatment. Vaccination with live vaccines is, however, not recommended. A live vaccine should not be administered until at least 6 months has elapsed after discontinuation of leflunomide.

Cholestyramine and activated charcoal

It is recommended that patients receiving leflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma levels of A771726 possibly by interruption of enterohepatic recycling and/or gastrointestinal dialysis.

Abnormal laboratory test results

None reported.

Food and alcohol

Given the potential for additive hepatotoxic effects, it is recommended that excessive alcohol consumption is avoided during treatment with leflunomide.

Overdosage

Signs and symptoms

There have been reports of chronic overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose and reports of acute overdose. There were no adverse events reported in the majority of case reports of overdose. Adverse events were consistent with the safety profile for leflunomide. The most frequent adverse events observed were diarrhoea, abdominal pain, leukopenia, anaemia and elevated liver function tests.

Management

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination. These wash-out procedures may be repeated if clinically necessary.

Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49 to 65% in 48 hours.

Administration of activated charcoal, as a suspension made of the powder, orally or via a nasogastric tube, 50 g every 6 hours for 24 hours, has been shown to reduce plasma concentrations of the active metabolite A771726 by 37% in 24 hours and by 48% in 48 hours.

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

Pharmaceutical precautions

Instructions for use/handling

Nil.

Incompatibilities

None known.

Special precautions for storage

Store at or below 25°C. Protect from light and moisture.

Medicine classification

Prescription Medicine.

Package quantities

Packs of 30 tablets in cartoned blister strips or HDPE bottles fitted with child resistant closures.

Further information

List of excipients

Lactose, maize starch, hydroxypropylcellulose, povidone, colloidal silicon dioxide, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, yellow iron oxide

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