

APO-LEFLUNOMIDE

1. APO-LEFLUNOMIDE (10mg and 20mg tablets)

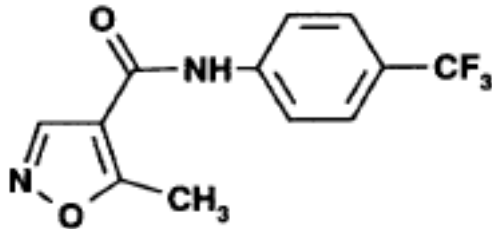
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Leflunomide 10mg or 20mg

Chemical Structure:

Leflunomide or N-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide), an isoxazole derivative.

Its empirical formula is $C_{12}H_9F_3N_2O_2$. The chemical structure of leflunomide is shown below:



Excipient(s) with known effect

Apo-Leflunomide do not contain gluten.

Apo-Leflunomide contain lactose

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APO-LEFLUNOMIDE 10mg are white, round, biconvex tablet engraved "LE" over "10" on one side and "APO" on the other side. Each tablet typically weighs 70mg.

APO-LEFLUNOMIDE 20mg are white, arc triangular shaped biconvex tablet, engraved "LE" over "20" on one side and "APO" on the other side. Each tablet typically weighs 140mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

APO-LEFLUNOMIDE is indicated for the treatment of:

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

4.2 Dose and method of administration

Loading Dose

Leflunomide therapy is started with a loading dose of 100mg 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 risk of haematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such similar medications in the recent past. (see "4.4 Special

warnings and precautions for use, Concomitant Use with Hepatotoxic and Haematotoxic Agents" and "Hepatotoxicity").

Maintenance Dose

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

Liver enzymes and haematological parameters must be monitored and dose adjustments or discontinuation may be necessary. (See "4.4 Special warnings and precautions for use"). 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 who have a serum creatinine concentration of $>133\mu\text{moles/L}$ (1.5mg/dL).

No dosage adjustment is required in the elderly.

Compatibility with other antirheumatic drugs

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

Please refer to the section "4.5 Interaction with other medicines and other forms of interactions" for information about co-administration with methotrexate and other hepatotoxic and haematotoxic drugs.

Method of administration

APO-LEFLUNOMIDE tablets should be swallowed whole with sufficient amount liquid. Absorption of leflunomide is not affected if it is taken with food. The tablets must NOT be divided.

4.3 Contraindications

APO-LEFLUNOMIDE must not be given to:

- patients with hypersensitivity to leflunomide, teriflunomide or to any of the excipients in the tablets (see "6.1 List of excipients")
- patients with severe immunodeficiency states, e.g. AIDS
- patients with significantly impaired bone marrow function or significant anaemia, leukopenia or thrombocytopenia due to causes other than rheumatoid arthritis
- patients with severe, uncontrolled infections
- patients with impairment of liver function
- pregnant women
- women of childbearing potential who are not using reliable contraception during treatment with APO-LEFLUNOMIDE and for a certain period of time thereafter, as long as plasma levels of A771726the active metabolite are above 0.02mg/L, unless undergoing washout treatment (see "4.6 Fertility, pregnancy and lactation")
- women who are breast-feeding
- patients with severe hypoproteinaemia
- patients who have, or have had Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme

4.4 Special warnings and precautions for use

Concomitant use with other Hepatotoxic and Haematotoxic Agents

Increased monitoring frequency is advised when leflunomide is used in combination with other hepatotoxic and haematotoxic agents (see "4.5 Interaction with other medicines and other forms of interaction").

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 has any evidence of pancytopenia on routine haematological monitoring, stop leflunomide, commence washout procedure and continue close haematological monitoring until confirmed resolution (see "4.9 Overdose").

Concomitant treatment with methotrexate and/or other hepatotoxic medications is associated with an increased risk of serious hepatic reactions. To minimise the risk of serious adverse reactions, it is essential that all monitoring recommendations are strictly adhered to. Concomitant use of teriflunomide and leflunomide is not recommended, as leflunomide is the parent compound of teriflunomide.

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.

Washout Procedure for Severe Adverse Reactions

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 (see "4.8 Undesirable 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 section "4.9 Overdose" and continued/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 cells and platelets) should be performed in all patients before the start of leflunomide treatment, and monthly for the first 6 months, followed by 6-8 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 occurrence of haematological reactions is increased.

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) and usually resolved while continuing treatment. Clinically significant elevations (>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 (see "4.4 Special warning and precautions for use, Liver function monitoring").

In the US4001 combination 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 received up to 48 weeks the addition of leflunomide to methotrexate therapy. In this study, patients with inadequate response to a stable dose of methotrexate for 6 months, were administered leflunomide with a loading dose of one 100mg tablet daily for 2 days and thereafter, patients received a maintenance dose of 10mg daily. These doses are both lower than the recommended initial dose of monotherapy with leflunomide. If dosing at 10mg/day was not well tolerated clinically, the dose was decreased to 10mg of leflunomide every other day. If the 10mg daily dose was tolerated, but disease activity persisted at 8 weeks or thereafter, the dose of leflunomide was increased to a maximum of 20mg daily. In the 6 month placebo-controlled study phase the incidence of ALT elevations >3 -fold ULN on leflunomide added to methotrexate therapy was 3.8% versus 0.8% when placebo was added to methotrexate. (The incidence of >3 -fold ULN ALT elevations for leflunomide monotherapy in study US301, MN301 and MN302 was 1.5% to 4.4%). ALT elevations <2 -fold ULN reversed to <2 -fold ULN and normalized to <1.2 -fold ULN with leflunomide dose reduction or discontinuation. Milder elevations of >1.2 to <2 -fold ULN normalized without change in leflunomide dose in most cases, although a minority normalized after dose reduction or discontinuation.

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 6-8 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 2-4 weeks.

For moderate elevations in ALT or AST (>2 -fold but <3 -fold ULN), closely monitor, with LFTs every 2-4 weeks and dosage reduction.

If ALT or AST elevations between 2- to 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.

Plasma Monitoring

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

Blood Pressure Monitoring

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

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 was found to be similar to 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 (see “4.5 Interaction with other medicines and other forms of interaction, Additional information on special populations”).

Skin Reactions

Cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and symptoms (DRESS) have been reported in patients treated with leflunomide (see “4.8 Undesirable effects”). If a patient taking leflunomide develops any of these skin conditions, therapy should be stopped and washout procedures should be initiated immediately (see “4.9 Overdose”).

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 (see “4.9 Overdose”).

Before starting treatment, all patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

Respiratory

Interstitial lung disease has been reported rarely during treatment with leflunomide (see “4.8 Undesirable Effects”). The risk of its occurrence is increased in patients with a history of interstitial lung disease. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnea, with or without fever may be a reason for further investigation. Discontinuation of the therapy and implementation of a washout with cholestyramine (see “4.9 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.

Peripheral neuropathy

Peripheral neuropathy has been reported rarely in patients receiving leflunomide. Most patients recovered after discontinuation of leflunomide, but some patients had persistent symptoms. For patients 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 perform the wash-out procedure (see “4.9 Overdose”).

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 (see “4.9 Overdose”). 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 rare reports of pancytopenia (rare), agranulocytosis (very rare) and thrombocytopenia (rare) in patients receiving leflunomide (see “4.4 Special warnings and precautions for use” “Concomitant use with hepatotoxic and haemotoxic agents”). 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 (see “4.4 Special warnings and precautions for use, 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 should be stopped and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide (see “4.9 Overdose”).

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 delay healing of accidental corneal lesions was observed. This effect may be attributed to the immunosuppressive effect of leflunomide. Its clinical relevance is, however, unclear.

Antigenicity

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

Mutagenicity

Leflunomide (A771726) was not mutagenic in bacteria (*Salmonella typhimurium* and *Escherichia coli*) or Chinese hamster ovary cell, did not cause chromosomal damage *in vivo* (mouse and Chinese hamster bone marrow cells), and did not induce unscheduled synthesis of DNA *in vitro* in mammalian cells. A minor metabolite of leflunomide, trifluoromethylaniline, was mutagenic and caused chromosomal damage *in vitro* assays, but did not cause chromosomal damage *in vivo* (Chinese hamster bone marrow cells) 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 15mg/kg/day [associated with plasma A771726 concentrations (AUC) similar to that expected in humans], an increase in bronchioalveolar adenomas in males given \geq 5mg/kg/day (A771726 AUC similar to or about 50% lower than that expected in

humans) and an increase in bronchioalveolar adenomas and carcinomas in females given 1.5mg/kg/day (A771726 AUC at least 10-20 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 6mg/kg/day (associated with A771726 AUC 25-65 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 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.

4.5 Interaction with other medicines and other forms of interaction

The enzymes involved in the metabolism of leflunomide and its metabolites are not precisely known. *In vitro* studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin and tolbutamide (see below). The extensive protein binding ability of A771726 could lead to displacement of other highly-bound drugs.

Cimetidine

An *in vivo* interaction study with cimetidine (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 (non-specific cytochrome P450 inducer) A771726 peak level were increased by approximately 40%, whereas the AUC was not significantly changed. The mechanism of this effect is unclear. Because of the potential for A771726 levels to continue to increase with multiple dosing, caution should be exercised if patients are to be receiving both leflunomide and rifampicin.

Warfarin

Increase 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.

Repeated doses of A771726 had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 is not an inhibitor or an inducer of CYP2C9. However, a decrease in peak international normalised ratio (INR) was observed when A771726 was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered, close INR follow-up and monitoring is recommended.

NSAIDs

NSAIDs (including COX-2 inhibitors) are known to cause hepatotoxicity, therefore caution is advised when leflunomide is used concomitantly (see "4.4 Special warnings and precautions for use"). Studies showed that ibuprofen and diclofenac did not displace A771726. A771726 displaced ibuprofen and diclofenac and the unbound fraction of these drugs was increased by 10%-50%. In clinical trials, no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered.

Tolbutamide

In vitro studies, A771726 was shown to cause increases ranging from 13% to 50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown. The unbound fraction of A771726 was increased 2-3 fold in the presence of tolbutamide.

Methotrexate

In a small (n=30) combination study of leflunomide (10-20mg/day) with methotrexate (10-25mg/week) co-administration increased the risk of hepatotoxicity. Baseline disease characteristics reflect a patient population with active RA (average tender and swollen joint count of 16) and longstanding disease (mean duration 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 two to three-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 ACR criteria for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa) (see "4.4 Special warnings and precautions for use", "Concomitant Use with Hepatotoxic and Haematotoxic Agents" and "Hepatotoxicity" sections).

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.

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

Tri-phasic Oral Contraceptives

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

Effect on oral contraceptive (0.03 mg ethinylestradiol and 0.15 mg levonorgestrel)

There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} and levonorgestrel C_{max} and AUC_{0-24} following repeated doses of A771726. While this interaction is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type of oral contraceptive treatment.

Vaccinations

No clinical data are available on the efficacy and safety of vaccinations under leflunomide treatment. Vaccination with live vaccines is, however, not recommended. A live vaccine should only be given after a period of at least 6 months has elapsed after stopping 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 A771726 (the

active metabolite of leflunomide) concentration. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of A771726.

Pharmacokinetic and Pharmacodynamics Interactions

The following pharmacokinetic and pharmacodynamic interaction studies were conducted with A771726 (principal active metabolite of leflunomide). As similar drug-drug interactions cannot be excluded for leflunomide at recommended doses, the following recommendations should be considered in patients treated with leflunomide:

Effect on repaglinide (CYP2C8 substrate)

There was an increase in mean repaglinide C_{max} and AUC following repeated doses of A771726, suggesting that A771726 is an inhibitor of CYP2C8 *in vivo*. Therefore, monitoring patients with concomitant use of drugs metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, is recommended as they may have higher exposure.

Effect on caffeine (CYP1A2 substrate)

Repeated doses of A771726 decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) suggesting that A771726 may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during concomitant treatment, as it could lead to the reduction of the efficacy of these products.

Effect on organic anion transporter 3 (OAT3) substrates

There was an increase in mean cefaclor C_{max} and AUC following repeated doses of A771726, suggesting that A771726 is an inhibitor of OAT3 *in vivo*. Therefore, when co-administered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

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

There was an increase in mean rosuvastatin C_{max} and AUC following repeated doses of A771726. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g. methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

Additional information on special populations

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 minimize any possible risk, men wishing to father a child should consider discontinuing use of leflunomide and taking cholestyramine 8 g 3 times daily for 11 days or 50 g activated charcoal 4 times daily for 11 days.

Pediatric 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 (see “5.3 Preclinical safety data, Clinical Trials” and “4.8 Undesirable Effects”)

Use in the Elderly

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

4.6 Fertility, pregnancy and lactation

Pregnancy

(Category X)

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, as long as the plasma levels of the active metabolite are above 0.02mg/L, unless washout treatment (waiting period or abbreviated wash-out period; see below). Pregnancy must be excluded before the start of 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 contraception. In a study in which leflunomide was given to healthy female volunteers concomitantly with a triphasic oral contraceptive pill containing 30mcg ethinyloestradiol, there was no reduction in the contraceptive activity of the pill, 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 day of menses, using the drug elimination procedure described below, the risk to the foetus may be decreased.

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.

Breast-feeding

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

Fertility

Oral administration of leflunomide at doses up to 4mg/kg/day plasma [A771726 concentrations (AUC) about 10-25 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 (plasma A771726 AUC similar to or much lower than expected in humans).

4.7 Effects on ability to drive and use machines

Leflunomide may cause dizziness and drowsiness. It is therefore advisable to exercise caution when driving, operating machinery, or engaging in other potentially hazardous activities.

4.8 Undesirable effects

In controlled studies, the following adverse events were reported, regardless of causality. Differences between leflunomide and placebo were observed for diarrhoea, elevated liver enzymes (ALT and AST), hair loss and rash.

Percentage of patients with adverse events \geq 3% in any leflunomide treated group							
	All RA Studies	Placebo-Controlled Studies				Active-Controlled Studies	
		MN301 and US301				MN302*	
	LEF (n=1339) ¹	LEF (n=315)	PL (n=210)	SSZ (n=133)	MTX (n=182)	LEF (n=501)	MTX (n=498)
BODY AS A WHOLE							
Allergic Reaction	2%	5%	2%	0%	6%	1%	2%
Asthenia	3%	6%	4%	5%	6%	3%	3%
Flu Syndrome	2%	4%	2%	0%	7%	0%	0%
Infection	4%	0%	0%	0%	0%	0%	0%
Injury Accident	5%	7%	5%	3%	11%	6%	7%
Pain	2%	4%	2%	2%	5%	1%	<1%
Abdominal Pain	6%	5%	4%	4%	8%	6%	4%
Back Pain	5%	6%	3%	4%	9%	8%	7%
CARDIOVASCULAR							
Hypertension ²	10%	9%	4%	4%	3%	10%	4%
Chest Pain	2%	4%	2%	2%	4%	1%	2%
GASTROINTESTINAL							
Anorexia	3%	3%	2%	5%	2%	3%	3%
Diarrhoea	17%	27%	12%	10%	20%	22%	10%
Dyspepsia	5%	10%	10%	9%	13%	6%	7%
Gastroenteritis	3%	1%	1%	0%	6%	3%	3%
Abnormal Liver Enzymes	5%	10%	2%	4%	10%	6%	17%
Nausea	9%	13%	11%	19%	18%	13%	18%
GI/Abdominal Pain	5%	6%	4%	7%	8%	8%	8%
Mouth Ulcer	3%	5%	4%	3%	10%	3%	6%
Vomiting	3%	5%	4%	4%	3%	3%	3%
METABOLIC AND NUTRITIONAL							
Hypokalemia	1%	3%	1%	1%	1%	1%	<1%

Weight Loss	4%	2%	1%	2%	0%	2%	2%
MUSCULOSKELETAL SYSTEM							
Arthralgia	1%	4%	3%	0%	9%	<1%	1%
Leg Cramps	1%	4%	2%	2%	6%	0%	0%
Joint Disorder	4%	2%	2%	2%	2%	8%	6%
Synovitis	2%	<1%	1%	0%	2%	4%	2%
Tenosynovitis	3%	2%	0%	1%	2%	5%	1%
NERVOUS SYSTEM							
Dizziness	4%	5%	3%	6%	5%	7%	6%
Headache	7%	13%	11%	12%	21%	10%	8%
Paresthesia	2%	3%	1%	1%	2%	4%	3%
RESPIRATORY SYSTEM							
Bronchitis	7%	5%	2%	4%	7%	8%	7%
Increased Cough	3%	4%	5%	3%	6%	5%	7%
Respiratory Infection	15%	21%	21%	20%	32%	27%	25%
Pharyngitis	3%	2%	1%	2%	1%	3%	3%
Pneumonia	2%	3%	0%	0%	1%	2%	2%
Rhinitis	2%	5%	2%	4%	3%	2%	2%
Sinusitis	2%	5%	5%	0%	10%	1%	1%
SKIN AND APPENDAGES							
Hair loss	10%	9%	1%	6%	6%	17%	10%
Eczema	2%	1%	1%	1%	1%	3%	2%
Pruritis	4%	5%	2%	3%	2%	6%	2%
Rash	10%	12%	7%	11%	9%	11%	10%
Dry Skin	2%	3%	2%	2%	0%	3%	1%
UROGENITAL SYSTEM							
Urinary Tract Infection	5%	5%	7%	4%	2%	5%	6%

*Only 10% of patients in MN302 received folate. All patients in US301 received folate.

- 1 Includes all controlled and uncontrolled trials with leflunomide.
- 2 Hypertension as a pre-existing condition was over-represented in all leflunomide treatment groups in Phase III trials. Analysis of new onset hypertension revealed no difference among the treatment groups.

In addition, the following adverse events have been reported in 1% to 3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

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, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder

<i>Endocrine:</i>	diabetes mellitus, hyperthyroidism
<i>Hemic and Lymphatic System:</i>	anemia (including iron deficiency anemia), ecchymosis, leukopenia, lymphadenopathy
<i>Metabolic and Nutritional:</i>	increased creatine phosphokinase, peripheral oedema, hyperglycaemia, hyperlipidaemia
<i>Musculoskeletal System:</i>	arthrosis, bursitis, muscle cramps, myalgia, bone necrosis, bone pain, tendon rupture
<i>Nervous System:</i>	anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweat, vertigo
<i>Respiratory System:</i>	asthma, dyspnea, epistaxis, lung disorder
<i>Skin and Appendages:</i>	acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, nail disorder, skin nodule, subcutaneous nodule, maculopapular rash, skin disorder, skin discoloration, ulcer skin
<i>Special Senses:</i>	blurred vision, cataract, conjunctivitis, eye disorder, taste perversion
<i>Urogenital System:</i>	albuminuria, cystitis, dysuria, hematuria, menstrual disorder, vaginal moniliasis, prostate disorder, urinary frequency.

Other less common adverse events seen in clinical trials include: one case of anaphylactic reaction occurred in Phase II following rechallenge of drug after withdrawal due to rash (rare); urticaria, transient thrombocytopenia (uncommon), eosinophilia (rare); and leukopenia $< 2 \times 10^9/L$ (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 (see "4.4 Special warnings and precautions for use"). 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 with the drug stopped.

Adverse events in paediatric patients with polyarticular course JRA:

The safety of leflunomide was studied in 74 patients with polyarticular course JRA, ranging in age from 3 to 17 years (47 patients from the active-controlled study and 27 from the open-label safety and pharmacokinetic study). The most common adverse events included abdominal pain, diarrhoea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache and dizziness. Less common adverse events included anaemia, hypertension and weight loss. Fourteen paediatric patients experience ALT and/or AST elevations, nine between 1.2 and 3-fold the upper limit of normal and five between 3 and 8-fold the upper limit of normal.

Post-marketing Experience

Adverse reactions reported during the post-marketing period are detailed below: These reactions are classified within body system categories using the following definitions:

Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000

Gastrointestinal system, liver

Common: Diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulcerations), abdominal pain, elevation of liver parameters (e.g. transaminases, less often gamma-GT, alkaline phosphatase, bilirubin), colitis including microscopic colitis

Allergic reactions, Skin and Appendages

Common: Mild allergic reactions (including maculopapular and other rashes), pruritus, eczema, dry skin, increased hair loss

Uncommon: Urticaria

Very rare: Severe anaphylactoid reactions. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme. In reports received so far, causal relationship with leflunomide treatment could not be established, but cannot be excluded. Vasculitis, including cutaneous necrotising vasculitis. Due to the underlying disease, a causal relationship could not be established.

Haemic and Lymphatic System

Uncommon: thrombocytopenia with platelet count $<100 \times 10^9/L$ ($<100G/L$)

Rare: eosinophilia, leukopenia (leukocytes $<2 G/l$), pancytopenia

Very rare: agranulocytosis

Liver

Rare: Hepatitis, jaundice/cholestasis

Very rare: Severe liver injury such as hepatic failure, and acute hepatic necrosis, that may be fatal, pancreatitis.

Infection

Rare: 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 give predispose patients to infection).

Cardiovascular

Common: Increase in blood pressure.

Not known: Pulmonary hypertension

Respiratory, Thoracic and Mediastinal Disorders

Rare: Interstitial lung disease (including interstitial pneumonitis), which can be fatal.

Nervous System

Common: headache, dizziness, paresthesia

Uncommon: Taste disturbances, anxiety.

Very rare: Peripheral neuropathy

Skin and subcutaneous tissue disorders

Very rare: Cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, drug reaction with eosinophilia and systemic symptoms (DRESS) (see section “4.4 *Special warnings and precautions for use*”)

Other

Common: Weight loss, asthenia

Recent, concomitant or consecutive use of potentially myelotoxic agents, may be associated with the risk of haematological effects.

Very rare cases of severe liver injury, 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

4.9 Overdose

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. There were no adverse events reported in the majority of case reports overdose. Adverse events were consistent with the safety profile for leflunomide. The most frequent adverse events observed were elevated diarrhoea, abdominal pain, 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. Cholestyramine given orally at a dose of 8g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49-65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50g 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.

These wash-out procedures may be repeated if clinically necessary.

Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicated that A771726 is not dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Immunosuppressants, ATC code: L04AA13

Mechanism of action

Leflunomide is an isoxazole immunomodulatory agent that is effective in animal models of arthritis and other autoimmune diseases, allergy and transplantation. *In vivo*, leflunomide is rapidly metabolized to the ring opened form, A771726, which is the active drug.

It has immunomodulating/immunosuppressive characteristics, acts as an antiproliferative agent, and displays weak anti-inflammatory properties. The antiproliferative activity is reversed by the addition of uridine to the cell culture, indicating that A771726 acts at the level of the pyrimidine biosynthesis pathway. 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. 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 septicæmia, leflunomide did not alter the resistance of mice to bacterial pathogens.

5.2 Pharmacokinetic properties

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 (~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 2 months of dosing.

There was evidence from multiple dosing studies in patients with rheumatoid arthritis that pharmacokinetics 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.

Pharmacokinetic parameters for A771726 after administration of Leflunomide at doses of 5, 10, 25 mg/day for 24 days to patients (n=54) with rheumatoid arthritis (mean ± SD) (study YU204):

Loading dose	50 mg	100 mg	100 mg
Maintenance dose	5 mg	10 mg	25 mg
C ₂₄ (day 1)	4.0 ± 0.6	8.4 ± 2.1	8.5 ± 2.2
C ₂₄ (ss) (mcg/mL) ²	8.8 ± 2.9	18 ± 9.6	63 ± 36
t _{1/2} (days)	15 ± 3	14 ± 5	18 ± 9

¹ Concentration at 24 hours after loading dose

² Concentration at 24 hours after maintenance doses at steady state

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 573mcg/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 11L).

Average plasma concentration of A771726 at steady state is approximately 30mcg/mL for a maintenance dose of 20mg/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 GI wall and the liver in metabolism.

In a study with radiolabelled (¹⁴C)-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 (TFMA) has been detected in the plasma of animals and man but concentrations were very low compared with A771726 (ng/ml compared to mcg/ml) and often below the limit of quantification. Concentrations in man were typically <10ng/mL whilst the highest recorded values were approximately 20ng/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 were eliminated in the urine and 48% were 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 (see “4.9 Overdose”). 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 chronic ambulatory peritoneal dialysis (CAPD) indicate that A771726 is not dialyzable.

After independent intravenous administration of A771726, clearance averaged 31mL/hr with an elimination half-life of 10 days. A similar clearance estimate (29 ± 17 mL/hr) was obtained from population pharmacokinetics analysis of RA patients enrolled in pivotal safety and efficacy studies.

Characteristics in specific groups of subjects or patients

Gender

Gender has not been shown to cause a consistent change in the *in vivo* pharmacokinetics of leflunomide and A771726.

Age

Age has been shown to cause a change in the *in vivo* pharmacokinetics of leflunomide and A771726 (see “Paediatric populations” below). Data in patients > 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 chronic ambulatory peritoneal dialysis (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. In the light of the fact 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 contra-indicated in patients with impairment of liver function.

Paediatric population

The pharmacokinetics of A771726 following oral administration of leflunomide have been investigated in 73 paediatric patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA) who ranged in age from 3 to 17 years. The results of a population pharmacokinetic of these trials have demonstrated that paediatric patients with body weights ~40kg have a reduced clearance of A771726 relative to adult rheumatoid arthritis patients.

Population Pharmacokinetic estimate of A771726 Clearance following oral administration of leflunomide in paediatric patients with polyarticular course JRA (Mean \pm SD [Range])		
N	Body Weight (kg)	CL (mL/h)
10	<20	18 \pm 9.8 [6.8-37]
30	20-40	18 \pm 9.5 [4.2-43]
33	>40	26 \pm 16 [69.7-93.6]

5.3 Preclinical safety data

Clinical Trials

Adult Rheumatoid Arthritis:

The efficacy of leflunomide in the treatment of rheumatoid arthritis has been demonstrated in three large, multicentre, long term clinical trials against placebo (PL), sulfasalazine (SSZ) and methotrexate (MTX). Of the patients receiving leflunomide, the majority received it for more than 336 days. The highest doses used for an extended period in the trials were leflunomide 20 mg/day, SSZ 2 g/day and MTX 15 mg/week. Study MN301 (leflunomide vs placebo vs sulfasalazine) was conducted in 2 parts: a 6 month comparison of the safety and efficacy of leflunomide vs placebo vs sulfasalazine followed by a 6 month extension study (MN303) to evaluate the effect of leflunomide on the progression of rheumatoid arthritis, in comparison to SSZ, by using X-rays of hands and feet to assess joint destruction. Study US301 (leflunomide vs placebo vs methotrexate with concomitant folic acid) was designed to compare the efficacy and safety of leflunomide in patients with active rheumatoid arthritis who had never previously received methotrexate. Study MN302 (leflunomide vs methotrexate without concomitant folic acid) was designed to compare the efficacy and safety of leflunomide vs methotrexate in patients with rheumatoid arthritis.

ACR criteria

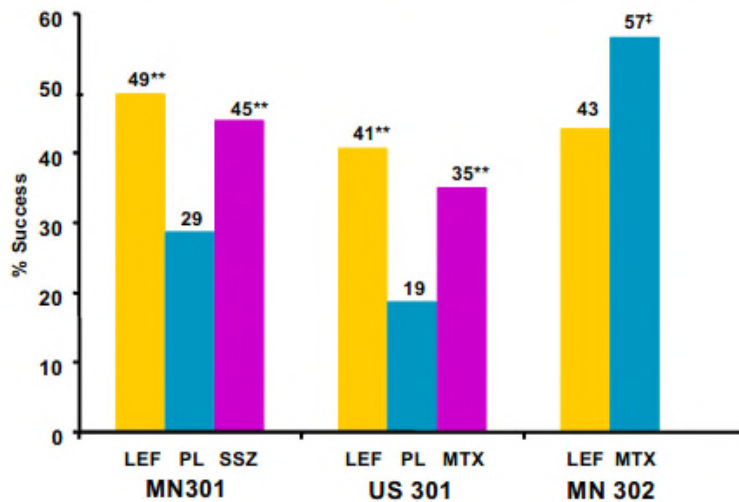
The outcome measures in these trials were: the “ACR Responder” rates over time, the “ACR Success” rates per treatment group, X-ray evaluation of disease progression, and health-related quality of life measures. An “ACR 20 Responder”, based upon American College of Rheumatology (ACR) criteria, is a patient with ~ 20% improvement in both tender and swollen joint count and in 3 of the following 5 criteria: physician global assessment, patient global assessment, function/disability measure, visual analog pain scale and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Similarly, an “ACR 50 Responder” and an “ACR 70 Responder” are respectively patients with ~50% and ~70% improvement in both tender and swollen joint count and in 3 of the following 5 criteria: physician global assessment, patient global assessment, function/disability measure, visual analog pain scale and ESR or CRP. An “ACR Success” is a patient who completes the trial and is an ACR Responder at the trial endpoint.

The clinical trials demonstrated a significant decrease in tender and swollen joint counts and scores, decreased morning stiffness and pain, improvement in patient and physician global assessments, increase in functional ability and improvement in quality of life [as measured by the Health Assessment Questionnaire (HAQ) and Modified Health Assessment Questionnaire (MHAQ)], retardation of joint destruction (as documented by X-ray analysis measuring both erosions and joint space narrowing), and a decrease in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF) levels. Clinical improvement started at approximately 4 weeks, usually stabilised within 4 to 6 months and was maintained for the duration of treatment.

Leflunomide demonstrated a consistent degree of efficacy across the 3 controlled trials. Leflunomide was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis. ACR 20 successes for leflunomide treatment in US301 and MN301 were

approximately twice that seen in placebo patients: 41% and 49% respectively in leflunomide-treated patients compared to 19% and 29% respectively in placebo-treated patients. Figure 1 displays ACR 20 Responder rates for each treatment group at endpoint.

Figure 1: ACR20 successes (responder at endpoint)

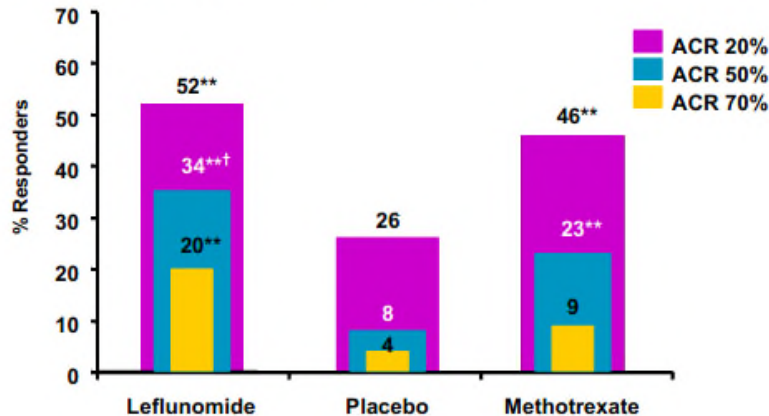


**p < 0.01 vs placebo, † p < 0.01 vs LEF

Comparisons	95% Confidence Interval	p value	
US301	Leflunomide vs Placebo	(12, 32)	<0.0001
	Methotrexate vs Placebo	(8, 30)	<0.0001
	Leflunomide vs Methotrexate	(-4, 16)	NS
MN301	Leflunomide vs Placebo	(7, 33)	0.0026
	Sulfasalazine vs Placebo	(4, 29)	0.0121
	Leflunomide vs Sulfasalazine	(-8, 16)	NS
MN302	Leflunomide vs Methotrexate	(-19, -7)	<0.0001

ACR 20, 50, and 70% response rates in all treatment groups of the US301 trial are shown in Figure 2. In US301, the ACR 20% response rate of patients treated with leflunomide was significantly increased from that seen in placebo-treated patients and similar to that seen in patients treated with methotrexate. Similarly, ACR 50% and 70% responses were approximately two times higher in patients treated with leflunomide or methotrexate than in patients who received placebo.

Figure 2: ACR response rates in US301



** p < 0.01 vs Placebo, † p < 0.05 vs MTX

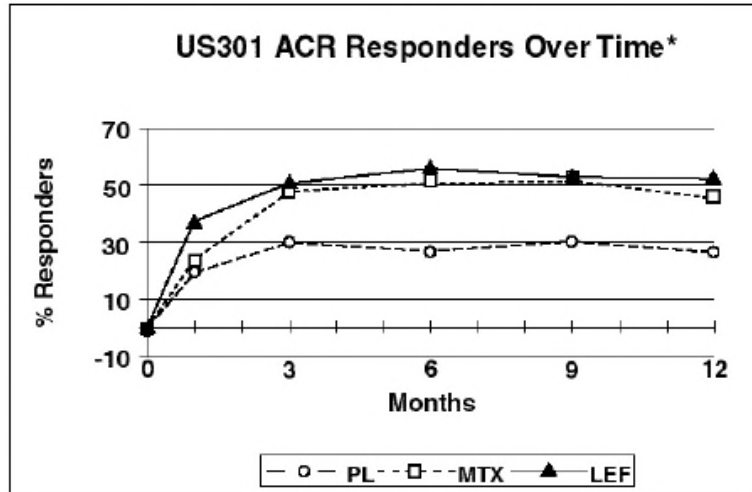
	Comparisons	95% Confidence Interval	p value
ACR 20	Leflunomide vs placebo	(15, 37)	<0.0001
	Methotrexate vs placebo	(9, 31)	0.0005
	Leflunomide vs methotrexate	(-4, 16)	NS
ACR 50	Leflunomide vs placebo	(18, 35)	<0.0001
	Methotrexate vs placebo	(7, 23)	0.0006
	Leflunomide vs methotrexate	(2, 21)	0.016
ACR 70	Leflunomide vs placebo	(9, 23)	0.0001
	Methotrexate vs placebo	(-0.3, 11)	NS
	Leflunomide vs methotrexate	(4, 18)	0.004

ACR response over time

ACR 20 Responder rate (%) vs Time in US301 is shown in Figure 3. This figure shows that:

- Leflunomide treatment was evident by 1 month, stabilized by 3-6 months and continued throughout the course of treatment
- Area Under Curve (AUC) analysis of ACR Responder vs Time demonstrated that leflunomide was statistically equivalent to the active comparator (methotrexate). No consistent differences were demonstrated
- Response rates over time showed an early and sustained response in leflunomide patients in all 3 trials (MN301, US 301, MN302)

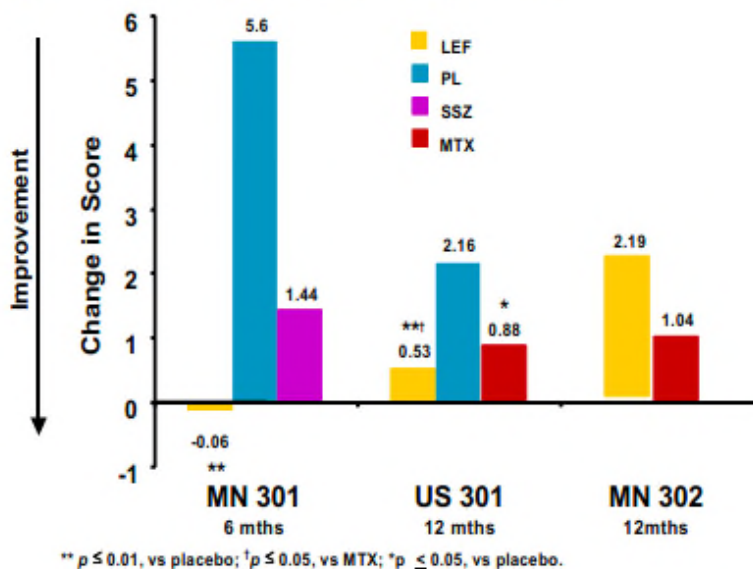
Figure 3



X-ray data

Figure 4 displays the change from baseline to endpoint in progression of disease as measured by the Sharp X-ray Score combining erosion and joint-space narrowing. Leflunomide was significantly superior to placebo in reducing the progression of disease as measured by the Sharp Score.

Figure 4: Change in total Sharp Score

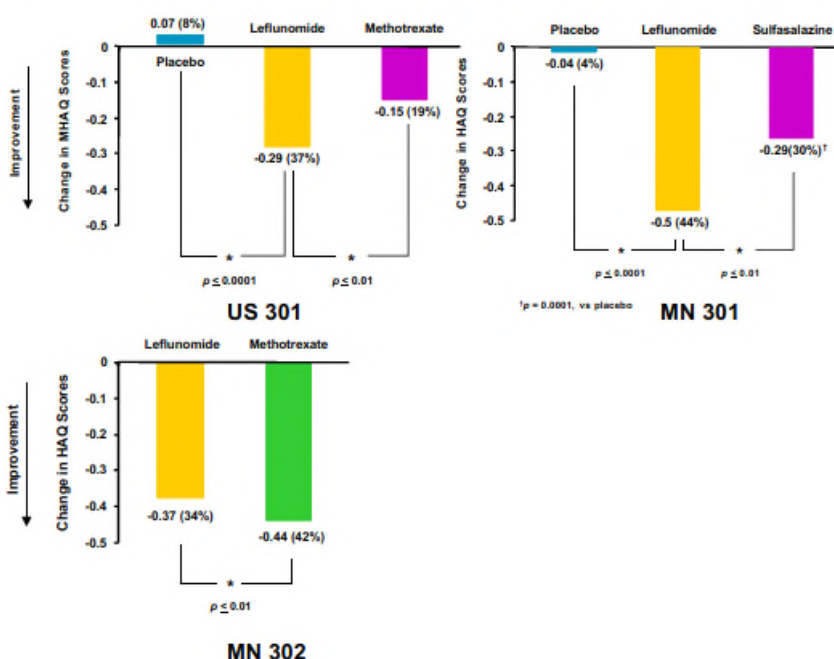


Comparisons	95% Confidence Interval	p Value
US301 Leflunomide vs Placebo	(-4.0, -1.1)	0.0007
Methotrexate vs Placebo	(-2.6, -0.2)	0.0187
Leflunomide vs Methotrexate	(-2.3, 0.0)	0.0494
MN301 Leflunomide vs Placebo	(-9.0, -1.4)	0.0081
Sulfasalazine vs Placebo	(-7.7, 0.0)	NS
Leflunomide vs Sulfasalazine	(-5.4, 2.3)	NS
MN302 Leflunomide vs Methotrexate	(-2.7, 8.0)	NS

Functional Ability/Quality of Life

The change in patients' functional ability as measured by the HAQ/MHAQ Disability Index is shown in Figure 5. The quality of life assessment carried out in MN301 and US301 showed that leflunomide was significantly superior to placebo. These studies also showed that leflunomide was significantly superior to SSZ and MTX in increasing the ability of subjects to perform activities of daily life. In MN302, MTX (without folic acid) achieved a greater response.

Figure 5: Change in functional ability (HAQ/MHAQ scores)



Paediatrics:

Leflunomide was studied in a single multicentre, double-blind, active-controlled trial in 94 patients (1:1 randomization) with polyarticular course juvenile rheumatoid arthritis (JRA) as defined by the American College of Rheumatology (ACR). Approximately 68% of paediatric patients receiving leflunomide, versus 89% of paediatric patients receiving the active comparator, improved by Week 16 (end of study) employing the JRA Definition of Improvement (DOI) \geq responder end-point. In this trial, the loading dose and maintenance dose of leflunomide was based on 3 weight categories: <20kg, 20-40kg and >40kg. The response rate to leflunomide in paediatric patients \leq 40kg was less robust in paediatric patients >40kg suggesting suboptimal dosing in smaller weight paediatric patients, as studied, resulting in less efficacious plasma concentration, despite reduced clearance of A771726 (see "5.2 Pharmacokinetic properties, Paediatric population").

Paediatric Population Pharmacokinetic Analysis: The pharmacokinetics of oral leflunomide have been investigated in 73 paediatric patients with polyarticular course JRA. The results of a population pharmacokinetic analysis demonstrated that there is a similarly wide inter-subject variability in the apparent total oral clearance in paediatric patients as in adults. Body weight was strongly correlated with the apparent volume of distribution [apparent volume of distribution (L) = 5.8 x (actual body weight/40kg)^{0.769}] and weakly correlated with apparent total oral clearance [apparent total oral clearance (L/h) = 0.02 x (actual body weight/40kg)^{0.43}] in paediatric patients with polyarticular course JRA. The half-life of A771726 decreased as body weight decreased.

Typical values for the apparent total oral clearance, apparent volume of distribution and half-life of A771726 at selected body weights in paediatric patients with polyarticular course JRA

Body Weight (kg)	Apparent Total Oral Clearance(L/h)	Apparent Volume of distribution (L)	Half-life (days)
10	0.011	2.00	5.2
20	0.015	3.40	6.6
30	0.018	4.65	7.6
40	0.020	5.80	8.4
50	0.022	6.89	9.0
60	0.024	7.92	9.6
70	0.025	8.92	10.1

The use of a loading dose may increase toxicity associated with leflunomide when used in children. The population pharmacokinetic data indicate that adult doses of leflunomide would be inappropriate in some children who would require a dose calculated from body weight. 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.

Psoriatic Arthritis:

The efficacy of leflunomide was demonstrated in a 6-month randomised, double-blind, placebo-controlled study in 188 Psoriatic Arthritis (PsA) patients. Adult patients with PsA were randomised to receive either leflunomide 100mg/day for 3 days followed by 20mg/day for the remainder of the period or placebo. In the leflunomide group, of the patients that were fully analysable (n=186), 59% had an improvement of the Psoriatic Arthritis Treatment Response Criteria (PsARC), the primary endpoint, compared with 29.7% in the placebo group (p<0.0001). The PsARC is a measure combining a physician global assessment, a patient global self-assessment, a joint pain/tenderness score and a joint swelling score. Improvement of the PsARC is defined as a decrease by ≥ 1 point for global assessments. An improvement of at least 2 of the above, one of which had to be joint pain/tenderness or joint swelling score and no worsening in any of the 4 measures was required to be considered a responder:

Mean Change in the Components of the PsARC Responder Index ^a			
Components	Placebo Controlled Study (6 Months)		
	LEF (n=95)	Placebo (n=91)	p-values
Joint Pain/Tenderness Score ^a	-9.1	-4.6	p<0.01
Joint Swelling Score ^a	-6.8	-4.2	p<0.01
Physician global Assessment – Improvement by at least 1 Category	52.6%	34.1%	p<0.01
Patient global Self-Assessment – Improvement by at least 1 Category	31.6%	30.8%	p<0.01

^aNegative Change Indicates Improvement

One 5-point Likert Scale (1= Very Good; 5 = Very Poor)

In a differing analysis which excluded some patients, the Psoriasis Area and Severity Index (PASI) was assessed to reflect changes in the extent and severity of psoriasis lesions as judged by erythema, desquamation, and infiltration. Leflunomide resulted in a significant improvement in PASI scores over the 24-week study relative to placebo, with a mean (\pm SD) improvement of 22.4% (\pm 51.6%) in the leflunomide group compared with a deterioration of 2.2% (\pm 70.4%) in the placebo group ($p=0.0030$).

PASI: Baseline Endpoint comparison of leflunomide versus placebo				
Variable	Mean (\pmSD)		Treatment Comparison ^a	
	Placebo	LEF	(p-value)	
PASI (FAS)	N=90	N=92		
Baseline	9.5 \pm 8.8	8.7 \pm 5.5		
Endpoint	8.8 \pm 8.7	6.6 \pm 6.5		
Change from baseline to endpoint	-0.6 \pm 6.1	-2.1 \pm 5.9	0.003	
PASI (PPS)	N=81	N=81		
Baseline	8.8 \pm 8.0	8.7 \pm 5.8		
Endpoint	8.3 \pm 8.3	6.2 \pm 6.1		
Change from baseline to endpoint	-0.5 \pm 6.3	-2.5 \pm 5.7	0.004	

^a p-values were calculated for difference between the treatment groups using ANOVA based on ranked percentage changes from baseline

Compared with the placebo group, a significantly greater proportion of patients in the leflunomide group experienced a \geq 50% reduction in PASI scores (PASI 50; 18.9% vs 30.4%; $p=0.050$) and \geq 75% reduction in PASI scores (PASI 75; 7.8% vs 17.4%; $p=0.048$) from baseline.

The efficacy of leflunomide in psoriatic arthritis has been assessed in a single study ($n=188$), and although the results of that study were statistically significant, supporting studies have not been performed. The efficacy of leflunomide in psoriatic arthritis patients has not been investigated beyond 6 months. The adverse events observed in the clinical study in PsA patients were comparable to the adverse events seen in the clinical trials in rheumatoid arthritis patients. Data on the safety of leflunomide in patients with PsA has been largely inferred from experience in patients with rheumatoid arthritis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-LEFLUNOMIDE 10mg and 20mg contain Lactose, Crospovidone, Magnesium Stearate, and Colloidal Silicon Dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 2 years from the date of manufacture

6.4 Special precautions

Store at or below 25°C

Protect from heat light and moisture.

6.5 Nature and contents of container

APO-LEFLUNOMIDE 10mg and 20mg: Bottles and /or blisters containing 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

14 February 2017

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new guideline for data sheet.