APPROVED
Order of Ministry of Health of Ukraine
28.04.2017 No. 478
Registration certificate No. UA/6367/01/02

AMENDED
Order of Ministry of Health of Ukraine
11.12.2023 № 2101

INSTRUCTION
for medical use

LEFNO®

Composition:
active substance: leflunomide;
1 tablet contains leflunomide 20 mg;
excipients: StarLac*, povidone, sodium croscarmellose, sodium lauryl sulfate, silicon dioxide colloidal anhydrous, talc, Kollicoat IR white II.
* StarLac: lactose monohydrate, maize starch.

Pharmaceutical form. Film-coated tablets.
Main physico-chemical properties: white oval-shaped biconvex film-coated tablet.

Pharmacotherapeutic group.
Immunosuppressants. ATC code L04A A13.

Pharmacological properties.
Pharmacodynamics.
Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties.
Leflunomide is effective in animal models of arthritis and of other autoimmune diseases and transplantation, mainly if administered during the sensitisation phase. It has immunomodulating/immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. Leflunomide exhibits the best protective effects on animal models of autoimmune diseases when administered in the early phase of the disease progression.
In vivo, leflunomide is rapidly and almost completely metabolised to A771726 which is active *in vitro*, and is presumed to be responsible for the therapeutic effect.
Mechanism of action.
A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.
Pharmacokinetic properties.
Leflunomide is rapidly converted to the active metabolite, A771726, by first-pass metabolism (ring opening) in gut wall and liver. In a study with radiolabelled 14C-leflunomide in three healthy volunteers, no unchanged leflunomide was detected in plasma, urine or feces. In other studies, unchanged leflunomide levels in plasma have rarely been detected. The only plasma-radiolabelled metabolite detected was A771726. This metabolite is responsible for essentially all the activity of leflunomide in the body.
Absorption

About 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. In multiple dose studies, the pharmacokinetic parameters of A771726 were linear over the dose range of 5 to 25 mg.
In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

In human plasma, A771726 is extensively bound to protein (albumin). The unbound fraction of A771726 is about 0.62%. Binding of A771726 is linear in the therapeutic concentration range. Binding of A771726 appeared slightly reduced and more variable in plasma from patients with rheumatoid arthritis or chronic renal insufficiency. The extensive protein binding of A771726 could lead to displacement of other highly-bound drugs. *In vitro* plasma protein binding interaction studies with warfarin at clinically relevant concentrations, however, showed no interaction. Similar studies showed that ibuprofen and diclofenac did not displace A771726, whereas the unbound fraction of A771726 is increased 2- to 3-fold in the presence of tolbutamide. A771726 displaced ibuprofen, diclofenac and tolbutamide but the unbound fraction of these medicinal products is only increased by 10% to 50%. There is no indication that these effects are of clinical relevance. Consistent with extensive protein binding A771726 has a low apparent volume of distribution (approximately 11 litres). There is no preferential uptake in erythrocytes.

Biotransformation

Leflunomide is metabolised to one primary (A771726) and many minor metabolites including TFMA (4-trifluoromethylaniline). The metabolic biotransformation of leflunomide to A771726 and subsequent metabolism of A771726 is not controlled by a single enzyme and has been shown to occur in microsomal and cytosolic cellular fractions. Interaction studies with cimetidine (non-specific cytochrome P450 inhibitor) and rifampicin (non-specific cytochrome P450 inducer), indicate that *in vivo* CYP enzymes are involved in the metabolism of leflunomide only to a small extent.

Elimination

Elimination of A771726 is slow and characterised by an apparent clearance of about 31 ml/hr. The elimination half-life in patients is approximately 2 weeks. After administration of a radiolabelled dose of leflunomide, radioactivity was equally excreted in feces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and feces 36 days after a single administration. 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 fecal component was A771726.
It has been shown in man that administration of an oral suspension of activated powdered charcoal or colestyramine leads to a rapid and significant increase in A771726 elimination rate and decline in plasma concentrations (see “Overdose” section). This is thought to be achieved by a gastrointestinal dialysis mechanism and/or by interrupting enterohepatic recycling.

Renal impairment

The pharmacokinetics of A771726 in patients on continuous peritoneal dialysis (CAPD) appeared to be similar to healthy volunteers. A more rapid elimination of A771726 was observed in hemodialysis subjects which was not due to extraction of medicinal product in the dialysate.

Hepatic impairment

No data are available regarding treatment of patients with hepatic impairment. The active metabolite A771726 is extensively protein bound and cleared via hepatic metabolism and biliary secretion. These processes may be affected by hepatic dysfunction.

Pediatric population
Pediatric patients with body weights ≤40 kg have a reduced systemic exposure (measured by C_{ss}) of A771726 relative to adult rheumatoid arthritis patients.
Elderly
Pharmacokinetic data in elderly (>65 years) are limited but consistent with pharmacokinetics in younger adults.

Clinical particulars.
Indications.
Treatment of active rheumatoid arthritis in adult patients with a disease-modifying antirheumatic drug (DMARD).
Treatment of active psoriatic arthritis in adult patients.
Recent or concurrent treatment with hepatotoxic or hematotoxic DMARDs (e.g., methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.
Moreover, switching from leflunomide to another DMARD without following the washout procedure (see "Special warnings and precautions for use" section) may also increase the risk of serious adverse reactions even for a long time after the switching.

Contraindications.
- Hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the leflunomide, to the principal active metabolite teriflunomide or to any of the excipients;
- impairment of liver function;
- severe immunodeficiency states, e.g., AIDS;
- significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis;
- serious infections;
- moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group;
- severe hypoproteinemia, e.g., in nephrotic syndrome;
- pregnancy;
- breastfeeding;
- use in women of childbearing potential who are not using reliable contraception during treatment with leflunomide and thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/L.

Pregnancy must be excluded before start of treatment with leflunomide!

Interaction with other medicinal products and other forms of interaction.
Interactions studies have only been performed in adults.
Increased side effects may occur in case of recent or concomitant use of hepatotoxic or hematotoxic medicinal products or when leflunomide treatment is followed by such medicinal products without a washout period. Therefore, closer monitoring of liver enzymes and hematological parameters is recommended in the initial phase after switching.
Methotrexate
In case of coadministration of leflunomide (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen. All elevations resolved, with continuation of both medicinal products or after discontinuation of leflunomide.
In patients with rheumatoid arthritis, no pharmacokinetic interaction between the leflunomide (10 to 20 mg per day) and methotrexate (10 to 25 mg per week) was demonstrated.
Vaccinations

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

Warfarin and other coumarin anticoagulants

There have been case reports of increased prothrombin time, when leflunomide and warfarin were coadministered. A pharmacodynamics interaction with warfarin was observed with A771726 metabolite. Therefore, when warfarin or another coumarin anticoagulant is coadministered, close international normalised ratio (INR) follow-up and monitoring is recommended.

NSAIDS/corticosteroids

If the patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide.

Colestyramine or activated charcoal

It is recommended that patients receiving leflunomide are not treated with colestyramine or activated powdered 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.

CYP450 inhibitors and inducers

In vitro inhibition studies in human liver microsomes suggest that cytochrome P450 (CYP) 1A2, 2C19 and 3A4 are involved in leflunomide metabolism. An interaction study with leflunomide and cimetidine (non-specific weak cytochrome P450 (CYP) inhibitor) has demonstrated a lack of a significant impact on A771726 exposure.

Following concomitant administration of a single dose of leflunomide to subjects receiving multiple doses of rifampicin (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.

Effect of leflunomide on other medicinal products

Oral contraceptives

When leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinylestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and A771726 metabolite pharmacokinetics were within predicted ranges. A pharmacokinetic interaction with oral contraceptives was observed with A771726.

The following study results of pharmacokinetic and pharmacodynamic interaction studies with A771726 (principal active metabolite of leflunomide) should be considered in patients treated with leflunomide, as similar drug-drug interactions cannot be excluded for leflunomide at recommended doses.

Effect on repaglinide (CYP2C8 substrate)

There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of A771726 metabolite, suggesting that A771726 is an inhibitor of CYP2C8 *in vivo*. Therefore, monitoring patients with concomitant use of medicinal products 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 metabolite decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that A771726 metabolite 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 treatment, as it could lead to the reduction of the efficacy of these products.

Effect on organic anion transporter 3 (OAT3) substrates

There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of A771726 metabolite, suggesting that A771726 is an inhibitor of OAT3 *in vivo*. Therefore, when coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin,

ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

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

There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of A771726 metabolite. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

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

There was an increase in mean ethinylestradiol C_{max} and $AUC_{0–24}$ (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and $AUC_{0–24}$ (1.33- and 1.41-fold, respectively) following repeated doses of A771726 metabolite. While this interaction is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type of oral contraceptive treatment.

Effect on warfarin (CYP2C9 substrate)

Repeated doses of A771726 metabolite had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 metabolite is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when A771726 metabolite was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is coadministered, close INR follow-up and monitoring is recommended.

Special warnings and precautions for use.

Concomitant administration of hepatotoxic or hematotoxic DMARDs (e.g., methotrexate) is not advisable.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g., hepatotoxicity, hematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped. Therefore, when such toxicities occur or if for any other reason A771726 metabolite needs to be cleared rapidly from the body, the washout procedure has to be followed. The procedure may be repeated as clinically necessary.

For washout procedures and other recommended actions in case of desired or unintended pregnancy, see “Pregnancy and lactation” section.

Liver reactions

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Cotreatment with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring and recommendations for their combined use are strictly adhered to.

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

For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and washout procedures initiated. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment, until liver enzyme levels have normalised.

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

Since the active metabolite of leflunomide, A771726, is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of A771726 are expected to be increased in patients with hypoproteinemia. Leflunomide is contraindicated in patients with severe hypoproteinemia or impairment of liver function (see "Contraindications" section).

Hematological reactions

Together with ALT, a complete blood cell count, including differential white blood cell count and platelets, must be performed before start of leflunomide treatment as well as every 2 weeks for the first 6 months of treatment and every 8 weeks thereafter.

In patients with pre-existing anemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of hematological disorders is increased. If such effects occur, a washout (see below) to reduce plasma levels of A771726 should be considered.

In case of severe hematological reactions, including pancytopenia, leflunomide and any concomitant myelosuppressive treatment must be discontinued and a leflunomide washout procedure initiated.

Combinations with other treatments

The use of leflunomide with antimalarials used in rheumatic diseases (e.g., chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents including tumor necrosis factor (TNF) alpha-Inhibitors has not been adequately studied up to now in randomised trials (with the exception of methotrexate, see "Interaction with other medicinal products and other forms of interaction" section). The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity (e.g., hepato- or hematotoxicity), combination with another DMARD (e.g., methotrexate) is not advisable.

Coadministration of teriflunomide with leflunomide is not recommended, as leflunomide is the parent compound of teriflunomide.

Switching to other treatments

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

Similarly, recent treatment with hepatotoxic or hematotoxic medicinal products (e.g., methotrexate) may result in increased side effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

Skin reactions

In case of ulcerative stomatitis, leflunomide administration should be discontinued.

Very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis and DRESS syndrome have been reported in patients treated with leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, leflunomide and any other possibly associated treatment must be discontinued, and a leflunomide washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contraindicated (see "Contraindications" section).

Pustular psoriasis and worsening of psoriasis have been reported after the use of leflunomide. Treatment withdrawal may be considered taking into account patient's disease and past history.

Skin ulcers can occur in patients during therapy with leflunomide. If leflunomide-associated skin ulcer is suspected or if skin ulcers persist despite appropriate therapy, leflunomide discontinuation and a complete washout procedure should be considered. The decision to resume leflunomide following skin ulcers should be based on clinical judgment of adequate wound healing.

Infections

It is known that medicinal products with immunosuppressive properties – like leflunomide – may cause patients to be more susceptible to infections, including opportunistic infections. Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe,

uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a washout procedure as described below.
Rare cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants.
Before starting treatment, all patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.
Patients with a history of tuberculosis should be carefully monitored because of the possibility of reactivation of the infection.

Respiratory reactions

Interstitial lung disease, as well as rare cases of pulmonary hypertension have been reported during treatment with leflunomide (see "Adverse reactions" section). The risk of their occurrence can be 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, may be a reason for discontinuation of the therapy and for further investigation, as appropriate.

Peripheral neuropathy

Cases of peripheral neuropathy have been reported in patients receiving leflunomide. Most patients improved after discontinuation of leflunomide. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking leflunomide develops a peripheral neuropathy, consider discontinuing therapy and performing the drug washout procedure (see "Special warnings and precautions for use" section).

Colitis

Colitis, including microscopic colitis has been reported in patients treated with leflunomide. In patients on leflunomide treatment presenting unexplained chronic diarrhea appropriate diagnostic procedures should be performed.

Blood pressure

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

Procreation (recommendations for men)

Male patients should be aware of the possible male-mediated fetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.
To date, there is no evidence on the risk of toxic effects on the embryo/fetus of the sperm of men who use leflunomide. However, animal studies to evaluate this specific risk have not been conducted. To minimise any possible risk, men wishing to father a child should consider discontinuing use of leflunomide and further washout procedure. In either case the A771726 plasma concentration should be measured twice (immediately after stopping the drug and again after an interval of at least 14 days). If both plasma concentrations are below 0.02 mg/L, and after a waiting period of at least 3 months, the risk of fetal toxicity is very low.

Washout procedure

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

Interference with determination of ionised calcium levels

The measurement of ionised calcium levels might show falsely decreased values under treatment with leflunomide and/or teriflunomide (the active metabolite of leflunomide) depending on the type of ionised calcium analyser used (e.g., blood gas analyser). Therefore, the plausibility of observed decreased ionised calcium levels needs to be questioned in patients under treatment with leflunomide or teriflunomide. In case of doubtful measurements, it is recommended to determine the total albumin adjusted serum calcium concentration.

Excipients

Lactose

The drug contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Maize starch

The drug contains maize starch, so it should not be used by patients with celiac disease (gluten enteropathy).

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Pregnancy and lactation.

Pregnancy

The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Lefno® is contraindicated in pregnancy.

Women of childbearing potential have to use effective contraception during and up to 2 years after treatment (see "Waiting period" below) or up to 11 days after treatment (see "Washout period" below).

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite, by instituting the drug washout procedure described below, at the first delay of menses may decrease the risk to the fetus from leflunomide.

In a small study in women who became inadvertently pregnant while taking leflunomide for no more than three weeks after conception and followed by a drug washout procedure, no significant differences were observed in the overall rate of major structural defects compared to either of the comparison groups (in the disease matched group and in healthy pregnant women).

For women receiving leflunomide treatment and who wish to become pregnant, one of the leflunomide washout procedures is recommended in order to ascertain that the fetus is not exposed to toxic concentrations of A771726 (target concentration below 0.02 mg/L).

Waiting period

A771726 plasma levels can be expected to be above 0.02 mg/L for a prolonged period. The concentration may be expected to decrease below 0.02 mg/L about 2 years after stopping the treatment with leflunomide. After a 2-year waiting period, the A771726 plasma concentration is measured for the first time. Thereafter, the A771726 plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/L no teratogenic risk is to be expected.

Washout procedure

After stopping treatment with leflunomide:

- colestyramine 8 g is administered 3 times daily for a period of 11 days;
- alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

However, also following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of 45 days between the first occurrence of the A771726 plasma concentration below 0.02 mg/L and fertilisation is required.

Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, prophylactic institution of a washout procedure may be advisable.

Both colestyramine and activated powdered charcoal may influence the absorption of estrogens and progestogens such that reliable contraception with oral contraceptives may not be 100% guaranteed during the washout procedure. Use of alternative contraceptive methods is recommended.

Breastfeeding

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breastfeeding women must, therefore, not receive leflunomide.

Fertility

Results of animal fertility studies have shown no effect on male and female fertility, but adverse effects on male reproductive organs were observed in repeated dose toxicity studies.

Effects on ability to drive and use machines.

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

Posology and method of administration.

The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:

- before initiation of leflunomide;
- every two weeks during the first six months of treatment;
- every 8 weeks thereafter (see "Special warnings and precautions for use" section).

The tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

Rheumatoid arthritis:

- the loading dose is 100 mg once daily for the first 3 days;
- the maintenance dose is 10 mg* to 20 mg once daily depending on the severity (activity) of the disease.

* If it is necessary to use a dose of 10 mg, tablets with the appropriate content of the active substance should be taken.

Omission of the loading dose may decrease the risk of adverse events (see "Pharmacological properties" section).

Psoriatic arthritis:

- the loading dose is 100 mg once daily for 3 days;
- the maintenance dose is leflunomide 20 mg once daily.

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

Patients with mild renal insufficiency: no dose adjustment is needed.

Patients above 65 years of age: no dose adjustment is needed.

Pediatric population.

The drug is not recommended for use in patients below 18 years since efficacy and safety in juvenile rheumatoid arthritis have not been established.

Overdose.

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 in adults and children. There were no adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: abdominal pain, nausea, diarrhea, elevated liver enzymes, anemia, leucopenia, pruritus and rash.

Management

In the event of an overdose or toxicity, colestyramine or charcoal is recommended to accelerate elimination. Colestyramine 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 (powder made into a suspension) orally or via nasogastric tube (50 g every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite A771726 by 37% in 24 hours and by 48% in 48 hours.
These washout procedures may be repeated if clinically necessary.
Studies with both hemodialysis and chronic ambulatory peritoneal dialysis indicate that A771726, the active metabolite of leflunomide, is not dialysable.

Adverse reactions.
Classification of expected frequencies of adverse reactions: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Infections and infestations:
rare – severe infections, including sepsis which may be fatal.
Like other agents with immunosuppressive potential, leflunomide may increase susceptibility to infections, including opportunistic infections (see "Special warnings and precautions for use" section). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).
Neoplasms benign, malignant and unspecified (cysts and polyps):
the risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.
Blood and lymphatic system disorders:
common – leucopenia (leucocytes >2 g/l);
uncommon – anemia, mild thrombocytopenia (platelets <100 g/l);
rare – pancytopenia (probably by antiproliferative mechanism), leucopenia (leucocytes <2 g/L), eosinophilia;
very rare – agranulocytosis.
Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of hematological effects.
Immune system disorders:
common – mild allergic reactions;
very rare – severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis.
Metabolism and nutrition disorders:
common – creatine phosphokinase increased;
uncommon – hypokalemia, hyperlipidemia, hypophosphatemia;
rare – lactate dehydrogenase increased;
not known – level of uric acid decreased (hypouricemia).
Psychiatric disorders:
uncommon – anxiety.
Nervous system disorders:
common – paresthesia, headache, dizziness, peripheral neuropathy.
Cardiac disorders:
common – mild increase in blood pressure;
rare – severe increase in blood pressure.
Respiratory, thoracic and mediastinal disorders:
rare – interstitial lung disease (including interstitial pneumonitis), which may be fatal;
not known – pulmonary hypertension.
Gastrointestinal disorders:
common – colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis, diarrhea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain;

uncommon – taste disturbances;
very rare – pancreatitis.
Hepatobiliary disorders:
common – elevation of liver parameters (alanine aminotransferase (ALT), gamma-glutamyl transferase, alkaline phosphatase, and bilirubin); hyperbilirubinemia;
rare – hepatitis, jaundice, cholestasis;
very rare – severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal.
Skin and subcutaneous tissue disorders:
common – increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin;
uncommon – urticaria;
very rare – toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme;
not known – cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis, drug reaction with eosinophilia and systemic symptoms (DRESS), skin ulcer.
Musculoskeletal and connective tissue disorders:
common – tendosynovitis;
uncommon – tendon rupture.
Renal and urinary disorders:
not known – renal failure.
Reproductive system and breast disorders:
not known – marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility.
General disorders and administration site conditions:
common – anorexia, weight loss (usually insignificant), asthenia.

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 3 years.

Storage conditions.
Store at the temperature below 25°C in the original package.
Keep out of reach of children.

Package.
10 tablets in blister, 3 blisters in carton pack.

Conditions of supply.
By prescription.

Manufacturer.
Kusum Healthcare Pvt Ltd.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Last revision date.