ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide medac 10 mg film-coated tablets
Leflunomide medac 15 mg film-coated tablets
Leflunomide medac 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Leflunomide medac 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of leflunomide.

Leflunomide medac 15 mg film-coated tablets
Each film-coated tablet contains 15 mg of leflunomide.

Leflunomide medac 20 mg film-coated tablets
Each film-coated tablet contains 20 mg of leflunomide.

Excipients with known effect

Leflunomide medac 10 mg film-coated tablets
Each film-coated tablet contains 76 mg of lactose (as monohydrate) and 0.06 mg of soya lecithin.

Leflunomide medac 15 mg film-coated tablets
Each film-coated tablet contains 114 mg of lactose (as monohydrate) and 0.09 mg of soya lecithin.

Leflunomide medac 20 mg film-coated tablets
Each film-coated tablet contains 152 mg of lactose (as monohydrate) and 0.12 mg of soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Leflunomide medac 10 mg film-coated tablets
White to almost white, round film-coated tablet with a diameter of about 6 mm.

Leflunomide medac 15 mg film-coated tablets
White to almost white, round film-coated tablet, debossed with “15” on one side with a diameter of about 7 mm.

Leflunomide medac 20 mg film-coated tablets
White to almost white, round film-coated tablet with a diameter of 8 mm and a break-mark on one side of the tablet. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with:
- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).
- active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure (see section 4.4) may also increase the risk of serious adverse reactions even for a long time after the switching.

4.2 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, and
- every 8 weeks thereafter (see section 4.4).

Posology
- In rheumatoid arthritis: leflunomide therapy is usually started with a loading dose of 100 mg once daily for 3 days. Omission of the loading dose may decrease the risk of adverse events (see section 5.1).
  The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.

- In psoriatic arthritis: leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days.
  The recommended maintenance dose is leflunomide 20 mg once daily (see section 5.1)

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

There is no dose adjustment recommended in patients with mild renal insufficiency.

No dosage adjustment is required in patients above 65 years of age.

Paediatric population
Leflunomide medac is not recommended for use in patients below 18 years since efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established (see sections 5.1 and 5.2).

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

4.3 Contraindications

- Hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the active substance, to the principal active metabolite teriflunomide, peanut or soya or to any of the excipients listed in section 6.1.

- Patients with impairment of liver function.

- Patients with severe immunodeficiency states, e.g. AIDS.

- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.

- Patients with serious infections (see section 4.4).

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

- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

- Pregnant women, or 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 (see section 4.6). Pregnancy must be excluded before start of treatment with leflunomide.

- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Concomitant administration of hepatotoxic or haematotoxic 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, haematotoxicity 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 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 section 4.6.

<u>Liver reactions</u>
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. Co-treatment with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations 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 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 wash-out 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 hypoproteinaemia. Leflunomide medac is contraindicated in patients with severe hypoproteinaemia or impairment of liver function (see section 4.3).

Haematological 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 anaemia, 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 haematological disorders is increased. If such effects occur, a washout (see below) to reduce plasma levels of A771726 should be considered.

In case of severe haematological reactions, including pancytopenia, Leflunomide medac 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 Tumour Necrosis Factor alpha-Inhibitors has not been adequately studied up to now in randomised trials (with the exception of methotrexate, see section 4.5). The risk associated with combination therapy, in particular in long-term treatment, is unknown. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato- or haematotoxicity), combination with another DMARD (e.g. methotrexate) is not advisable.

Co-administration of teriflunomide 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 haematotoxic medicinal products (e.g. methotrexate) may result in increased side effects; therefore, the initiation of leflunomide treatment has to carefully be considered regarding these benefit/risk aspects and closer monitoring is recommended in the initial phase after switching.

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

Very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) 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 medac 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 section 4.3).

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.

Impaired wound-healing after surgery can occur in patients during therapy with leflunomide. Based on an individual assessment, it may be considered to interrupt leflunomide treatment in the peri-surgical

period and administer a washout procedure as described below. In case of interruption, the decision to resume leflunomide 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 and pulmonary nodules have been reported during treatment with leflunomide (see section 4.8). The risk of interstitial lung disease and pulmonary hypertension 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 dyspnoea, 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 medac. Most patients improved after discontinuation of Leflunomide medac. 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 medac develops a peripheral neuropathy, consider discontinuing Leflunomide medac therapy and performing the drug elimination procedure (see section 4.4).

Colitis

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

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 foetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.

There are no specific data on the risk of male-mediated foetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimise any possible risk, men wishing to father a child should consider discontinuing use of leflunomide and taking colestyramine 8 g 3 times daily for 11 days or 50 g of activated powdered charcoal 4 times daily for 11 days.

In either case the A771726 plasma concentration is then 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, and after a waiting period of at least 3 months, the risk of foetal 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
Leflunomide medac contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Soya lecithin
Leflunomide medac contains soya lecithin. If a patient is hypersensitive to peanut or soya, Leflunomide medac must not be used.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 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 haematotoxic medicinal products or when leflunomide treatment is followed by such medicinal products without a washout period (see also guidance concerning combination with other treatments, section 4.4). Therefore, closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

Methotrexate
In a small (n = 30) study with co-administration of leflunomide (10 to 20 mg per day) with methotrexate (10 to 25 mg per week) a 2- to 3-fold elevation in liver enzymes was seen on 5 of 30 patients. All elevations resolved, 2 with continuation of both medicinal products and 3 after discontinuation of leflunomide. A more than 3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both medicinal products and 3 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 Leflunomide medac.

Warfarin and other coumarin anticoagulants
There have been case reports of increased prothrombin time, when leflunomide and warfarin were co-administered. A pharmacodynamics interaction with warfarin was observed with A771726 in a clinical pharmacology study (see below). Therefore, when warfarin or another coumarin anticoagulant is co-administered, 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.

Effect of other medicinal products on leflunomide

Cholestyramine 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; see also section 5) 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 *in vivo* 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
In a study in which leflunomide was given concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinyloestradiol to healthy female volunteers, there was no reduction in contraceptive activity of the pill, and A771726 pharmacokinetics were within predicted ranges. A pharmacokinetic interaction with oral contraceptives was observed with A771726 (see below).

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 study results and 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 (1.7- and 2.4-fold, respectively), following repeated doses of A771726, 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 decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18 % and 55 %, respectively, 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 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, 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 (Breast Cancer Resistance Protein) 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. 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. 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 had no effect on the pharmacokinetics of S-warfarin, indicating that A771726 is not an inhibitor or an inducer of CYP2C9. However, a 25 % 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
The active metabolite of leflunomide, A771726 is suspected to cause serious birth defects when administered during pregnancy. Leflunomide medac is contraindicated during pregnancy (see section 4.3).

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 abbreviated “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 elimination procedure described below, at the first delay of menses may decrease the risk to the foetus from leflunomide.

In a small prospective study in women (n = 64) who became inadvertently pregnant while taking leflunomide for no more than three weeks after conception and followed by a drug elimination procedure, no significant differences (p = 0.13) were observed in the overall rate of major structural defects (5.4 %) compared to either of the comparison groups (4.2 % in the disease matched group [n = 108] and 4.2 % in healthy pregnant women [n = 78]).

For women receiving leflunomide treatment and who wish to become pregnant, one of the following procedures is recommended in order to ascertain that the foetus 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.

For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

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 one-and-a-half months between the first occurrence of a 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 oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Breast-feeding
Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding 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 (see section 5.3).

4.7 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.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse effects with leflunomide are: mild increase in blood pressure, leucopenia, paraesthesia, headache, dizziness, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain, increased hair loss, eczema, rash (including maculo-papular rash), pruritus, dry skin, tenosynovitis, CPK increased, anorexia, weight

loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatise, bilirubin).

Classification of expected frequencies:
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 also section 4.4). Thus, the overall incidence of infections can increase (in particular of rhinitis, bronchitis and pneumonia).

Neoplasms benign, malignant and unspecified (incl 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: anaemia, 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 haematological effects.

Immune system disorders
Common: mild allergic reactions
Very rare: severe anaphylactic/anaphylactoid reactions, vasculitis, including cutaneous necrotizing vasculitis

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

Psychiatric disorders
Uncommon: anxiety

Nervous system disorders
Common: paraesthesia, 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, pulmonary nodule

Gastrointestinal disorders

Common:	colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis, diarrhoea, 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 (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)
Rare:	hepatitis, jaundice/cholestasis
Very rare:	severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

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:	tenosynovitis
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking Leflunomide medac 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, diarrhoea, elevated liver enzymes, anaemia, 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 CAPD (chronic ambulatory peritoneal dialysis) indicate that A771726, the primary metabolite of leflunomide, is not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, ATC code: L04AK01.

Human pharmacology
Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties.

Animal pharmacology
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, it 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.

Clinical efficacy and safety

Rheumatoid arthritis
The efficacy of leflunomide in the treatment of rheumatoid arthritis was demonstrated in 4 controlled trials (1 in phase II and 3 in phase III). The phase II trial, study YU203, randomised 402 subjects with active rheumatoid arthritis to placebo (n = 102), leflunomide 5 mg (n = 95), 10 mg (n = 101) or 25 mg/day (n = 104). The treatment duration was 6 months.
All leflunomide patients in the phase III trials used an initial dose of 100 mg for 3 days.
Study MN301 randomised 358 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n = 133), sulphasalazine 2 g/day (n = 133), or placebo (n = 92). Treatment duration was 6 months.
Study MN303 was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulphasalazine.
Study MN302 randomised 999 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n = 501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n = 498). Folate supplementation was optional and only used in 10 % of patients. Treatment duration was 12 months.
Study US301 randomised 482 subjects with active rheumatoid arthritis to leflunomide 20 mg/day (n = 182), methotrexate 7.5 mg/week increasing to 15 mg/week (n = 182), or placebo (n = 118). All patients received folate 1 mg bid. Treatment duration was 12 months.

Leflunomide at a daily dose of at least 10 mg (10 to 25 mg in study YU203, 20 mg in studies MN301 and US301) was statistically significantly superior to placebo in reducing the signs and symptoms of rheumatoid arthritis in all 3 placebo-controlled trials. The ACR (American College of Rheumatology) response rates in study YU203 were 27.7 % for placebo, 31.9 % for 5 mg, 50.5 % for 10 mg and 54.5 % for 25 mg/day. In the phase III trials, the ACR response rates for leflunomide 20 mg/day vs. placebo were 54.6 % vs. 28.6 % (study MN301), and 49.4 % vs. 26.3 % (study US301). After

12 months with active treatment, the ACR response rates in leflunomide patients were 52.3 % (studies MN301/303), 50.5 % (study MN302) and 49.4 % (study US301), compared to 53.8 % (studies MN301/303) in sulphasalazine patients, 64.8 % (study MN302), and 43.9 % (study US301) in methotrexate patients. In study MN302 leflunomide was significantly less effective than methotrexate. However, in study US301 no significant differences were observed between leflunomide and methotrexate in the primary efficacy parameters. No difference was observed between leflunomide and sulphasalazine (study MN301). The leflunomide treatment effect was evident by 1 month, stabilised by 3 to 6 months and continued throughout the course of treatment.

A randomised, double-blind, parallel-group non-inferiority study compared the relative efficacy of two different daily maintenance doses of leflunomide, 10 mg and 20 mg. From the results it can be concluded that efficacy results of the 20 mg maintenance dose were more favourable, on the other hand, the safety results favoured the 10 mg daily maintenance dose.

Paediatric population
Leflunomide was studied in a single multicenter, randomized, double-blind, active-controlled trial in 94 patients (47 per arm) with polyarticular course juvenile rheumatoid arthritis. Patients were 3-17 years of age with active polyarticular course JRA regardless of onset type and naive to methotrexate or leflunomide. In this trial, the loading dose and maintenance dose of leflunomide was based on three weight categories: < 20 kg, 20 - 40 kg, and > 40 kg. After 16 weeks treatment, the difference in response rates was statistically significant in favour of methotrexate for the JRA Definition of Improvement (DOI) ≥ 30 % ($p = 0.02$). In responders, this response was maintained during 48 weeks (see section 4.2).
The pattern of adverse events of leflunomide and methotrexate seems to be similar, but the dose used in lighter subjects resulted in a relatively low exposure (see section 5.2). These data do not allow an effective and safe dose recommendation.

Psoriatic arthritis
The efficacy of leflunomide was demonstrated in one controlled, randomised, double blind study 3L01 in 188 patients with psoriatic arthritis, treated at 20 mg/day. Treatment duration was 6 months.

Leflunomide 20 mg/day was significantly superior to placebo in reducing the symptoms of arthritis in patients with psoriatic arthritis: the PsARC (Psoriatic Arthritis treatment Response Criteria) responders were 59 % in the leflunomide group and 29.7 % in the placebo group by 6 months ($p < 0.0001$). The effect of leflunomide on improvement of function and on reduction of skin lesions was modest.

Postmarketing studies
A randomised study assessed the clinical efficacy response rate in DMARD-naïve patients (n = 121) with early RA, who received either 20 mg or 100 mg of leflunomide with matching placebo in two parallel groups during the initial three day double blind period. The initial period was followed by an open label maintenance period of three months, during which both groups received leflunomide 20 mg daily. The efficacy of leflunomide was confirmed in this study, but no incremental overall benefit was observed in the studied population with the use of a loading dose regimen. The safety data obtained from both treatment groups were consistent with the known safety profile of leflunomide, however, the incidence of gastrointestinal adverse events and of elevated liver enzymes tended to be higher in the patients receiving the loading dose of 100 mg leflunomide.

5.2 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 ^{14}C-leflunomide in three healthy volunteers, no unchanged leflunomide was detected in plasma, urine or faeces. In other studies, unchanged leflunomide levels in plasma have rarely been detected, however, at ng/ml plasma levels. The only plasma-radiolabelled metabolite detected was A771726. This metabolite is responsible for essentially all the *in-vivo* activity of Leflunomide medac.

Absorption

Excretion data from the ^{14}C study indicated that at least 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 in patients with rheumatoid arthritis, 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 drugs 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 faeces, probably by biliary elimination, and in urine. A771726 was still detectable in urine and faeces 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 faecal 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 section 4.9). This is thought to be achieved by a gastrointestinal dialysis mechanism and/or by interrupting enterohepatic recycling.

Renal impairment

Leflunomide was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of A771726 in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of A771726 was observed in haemodialysis 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.

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 analysis of these trials have demonstrated that paediatric patients with body weights ≤ 40 kg have a reduced systemic exposure (measured by C_{ss}) of A771726 relative to adult rheumatoid arthritis patients (see section 4.2).

Elderly
Pharmacokinetic data in elderly (> 65 years) are limited but consistent with pharmacokinetics in younger adults.

5.3 Preclinical safety data

Leflunomide, administered orally and intraperitoneally, has been studied in acute toxicity studies in mice and rats. Repeated oral administration of leflunomide to mice for up to 3 months, to rats and dogs for up to 6 months and to monkeys for up to 1 month's duration revealed that the major target organs for toxicity were bone marrow, blood, gastrointestinal tract, skin, spleen, thymus and lymph nodes. The main effects were anaemia, leucopenia, decreased platelet counts and panmyelopathy and reflect the basic mode of action of the compound (inhibition of DNA synthesis). In rats and dogs, Heinz bodies and/or Howell-Jolly bodies were found. Other effects found on heart, liver, cornea and respiratory tract could be explained as infections due to immunosuppression. Toxicity in animals was found at doses equivalent to human therapeutic doses.

Leflunomide was not mutagenic. However, the minor metabolite TFMA (4-trifluoromethylaniline) caused clastogenicity and point mutations in vitro, whilst insufficient information was available on its potential to exert this effect *in vivo*.

In a carcinogenicity study in rats, leflunomide did not show carcinogenic potential. In a carcinogenicity study in mice an increased incidence of malignant lymphoma occurred in males of the highest dose group, considered to be due to the immunosuppressive activity of leflunomide. In female mice an increased incidence, dose-dependent, of bronchiolo-alveolar adenomas and carcinomas of the lung was noted. The relevance of the findings in mice relative to the clinical use of leflunomide is uncertain.

Leflunomide was not antigenic in animal models.
Leflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range and exerted adverse effects on male reproductive organs in repeated dose toxicity studies. Fertility was not reduced.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
lactose monohydrate
low-substituted hydroxypropyl cellulose
tartaric acid
sodium laurylsulfate
magnesium stearate

Film-coating
lecithin (soybeans)
poly(vinyl alcohol)
talc
titanium dioxide (E 171)
xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Leflunomide medac 10 mg film-coated tablets
40 ml HDPE-wide-necked bottle, with screw cap with integrated desiccant container (white silica gel), containing either 30, 60 or 100 film-coated tablets per container.

Leflunomide medac 15 mg film-coated tablets
40 ml HDPE-wide-necked bottle, with screw cap with integrated desiccant container (white silica gel), containing either 30, 60, 90 or 100 film-coated tablets per container.

Leflunomide medac 20 mg film-coated tablets
40 ml HDPE-wide-necked bottle, with screw cap with integrated desiccant container (white silica gel), containing either 15, 30, 60 or 100 film-coated tablets per container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Leflunomide medac 10 mg film-coated tablets
EU/1/10/637/001 (30 tablets)
EU/1/10/637/002 (60 tablets)
EU/1/10/637/004 (100 tablets)

Leflunomide medac 15 mg film-coated tablets
EU/1/10/637/010 (30 tablets)
EU/1/10/637/011 (60 tablets)
EU/1/10/637/012 (90 tablets)
EU/1/10/637/013 (100 tablets)

Leflunomide medac 20 mg film-coated tablets
EU/1/10/637/005 (15 tablets)
EU/1/10/637/006 (30 tablets)
EU/1/10/637/007 (60 tablets)
EU/1/10/637/009 (100 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2010
Date of latest renewal: 23 March 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The marketing authorisation holder (MAH) shall ensure that all physicians who are expected to prescribe/use Leflunomide medac are provided with a physician educational pack containing the following:
- The Summary of Product Characteristics

- Physician Leaflet

The Physician Leaflet should contain the following key messages:

- That there is a risk of severe liver injury and so regular measurement of ALT (SGPT) levels to monitor liver function is important. The information provided in the Physician Leaflet should provide information on dose reduction, discontinuation and wash out procedures.
- The identified risk of synergistic hepato- or haematotoxicity associated with combination therapy with another Disease-Modifying Antirheumatic Drug (e.g. methotrexate).
- That there is a risk of teratogenicity and so pregnancy must be avoided until leflunomide plasma levels are at an appropriate level. Physicians and patients should be made aware that there is an ad hoc advisory service available to provide information on leflunomide plasma level laboratory testing.
- The risk of infections, including opportunistic infections, and the contraindication for use in immuno-compromised patients.
- The need to counsel patients on important risks associated with leflunomide therapy and appropriate precautions when using the medicine.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER PACKAGING/BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide medac 10 mg film-coated tablets
Leflunomide medac 15 mg film-coated tablets
Leflunomide medac 20 mg film-coated tablets

leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of leflunomide.
Each film-coated tablet contains 15 mg of leflunomide.
Each film-coated tablet contains 20 mg of leflunomide.

3. LIST OF EXCIPIENTS

This medicinal product contains lactose and soya lecithin (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

<film-coated tablet>

<Leflunomide medac 10 mg:>
30 film-coated tablets
60 film-coated tablets
100 film-coated tablets

<Leflunomide medac 15 mg:>
30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets

<Leflunomide medac 20 mg:>
15 film-coated tablets
30 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/637/001 (10 mg, 30 tablets)
EU/1/10/637/002 (10 mg, 60 tablets)
EU/1/10/637/004 (10 mg, 100 tablets)

EU/1/10/637/005 (20 mg, 15 tablets)
EU/1/10/637/006 (20 mg, 30 tablets)
EU/1/10/637/007 (20 mg, 60 tablets)
EU/1/10/637/009 (20 mg, 100 tablets)

EU/1/10/637/010 (15 mg, 30 tablets)
EU/1/10/637/011 (15 mg, 60 tablets)
EU/1/10/637/012 (15 mg, 90 tablets)
EU/1/10/637/013 (15 mg, 100 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Leflunomide medac 10 mg
Leflunomide medac 15 mg
Leflunomide medac 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide medac 10 mg film-coated tablets
Leflunomide medac 15 mg film-coated tablets
Leflunomide medac 20 mg film-coated tablets

leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of leflunomide.
Each film-coated tablet contains 15 mg of leflunomide.
Each film-coated tablet contains 20 mg of leflunomide.

3. LIST OF EXCIPIENTS

This medicinal product contains lactose and soya lecithin (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

<film-coated tablet>

<Leflunomide medac 10 mg:>
30 film-coated tablets
60 film-coated tablets
100 film-coated tablets

<Leflunomide medac 15 mg:>
30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets

<Leflunomide medac 20 mg:>
15 film-coated tablets
30 film-coated tablets
60 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/637/001 (10 mg, 30 tablets)
EU/1/10/637/002 (10 mg, 60 tablets)
EU/1/10/637/004 (10 mg, 100 tablets)

EU/1/10/637/005 (20 mg, 15 tablets)
EU/1/10/637/006 (20 mg, 30 tablets)
EU/1/10/637/007 (20 mg, 60 tablets)
EU/1/10/637/009 (20 mg, 100 tablets)

EU/1/10/637/010 (15 mg, 30 tablets)
EU/1/10/637/011 (15 mg, 60 tablets)
EU/1/10/637/012 (15 mg, 90 tablets)
EU/1/10/637/013 (15 mg, 100 tablets)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Leflunomide medac 10 mg film-coated tablets
leflunomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Leflunomide medac is and what it is used for

Leflunomide medac belongs to a group of medicines called anti-rheumatic medicines. It contains the active substance leflunomide.

Leflunomide medac is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis.

Symptoms of rheumatoid arthritis include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (lack of red blood cells).

Symptoms of active psoriatic arthritis include inflammation of joints, swelling, difficulty in moving, pain, and patches of red, scaly skin (skin lesions).

2. What you need to know before you take Leflunomide medac

Do not take Leflunomide medac
- if you have ever had an **allergic** reaction to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome), peanut or soya or to any of the other ingredients of this medicine (listed in section 6), or if you are allergic to teriflunomide (used to treat multiple sclerosis),
- if you have any **liver problems**,
- if you have moderate to severe **kidney problems**,
- if you have severely low numbers of **proteins in your blood** (hypoproteinaemia),
- if you suffer from any problem which affects your **immune system** (e.g. AIDS),
- if you have any problem with your **bone marrow,** or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets,
- if you are suffering from a **serious infection**,
- if you are **pregnant**, think you may be pregnant, or are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Leflunomide medac
- if you have ever suffered from **inflammation of the lung** (interstitial lung disease**)**,
- if you have ever had **tuberculosis** or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis.
- if you are **male** and wish to father a child. As it cannot be excluded that Leflunomide medac passes into semen, reliable contraception should be used during treatment with Leflunomide medac. Men wishing to father a child should contact their doctor who may advise them to stop taking Leflunomide medac and take certain medicines to remove Leflunomide medac rapidly and sufficiently from their body. You will then need a blood test to make sure that Leflunomide medac has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.
- if you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.
- if you will have or have had recent major surgery, or if you still have an unhealed wound following surgery. Leflunomide medac may impair wound healing.

Leflunomide medac can occasionally cause some problems with your blood, liver, lungs or nerves in your arms or legs. It may also cause some serious allergic reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), or increase the chance of a severe infection. For more information on these, please read section 4 (Possible side effects).

DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

Your doctor will carry out **blood tests** at regular intervals, before and during treatment with Leflunomide medac, to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as Leflunomide medac can cause an increase in blood pressure.

Tell your doctor if you have unexplained chronic diarrhoea. Your doctor may perform additional tests for differential diagnosis.

Tell your doctor if you develop skin ulcer during treatment with Leflunomide medac (see also section 4).

Children and adolescents
Leflunomide medac is not recommended for use in children and adolescents below 18 years of age.

Other medicines and Leflunomide medac
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

This is especially important if you are taking:
- other medicines for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate) as these combinations are not advisable,
- warfarin and other oral medicines used to thin the blood, as monitoring is necessary to reduce the risk of side effects of this medicine
- teriflunomide for multiple sclerosis
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhoea

- theophylline for asthma
- tizanidine, a muscle relaxant
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indomethacin, ketoprofen for pain or inflammation
- furosemide for heart disease (diuretic, water pill)
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- a medicine called colestyramine (used to reduce high cholesterol) or activated charcoal as these medicines can reduce the amount of Leflunomide medac which is absorbed by the body.

If you are already taking a non-steroidal **anti-inflammatory** drug (NSAID) and/or **corticosteroids**, you may continue to take them after starting Leflunomide medac.

Vaccinations
If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking Leflunomide medac, and for a certain amount of time after stopping treatment.

Leflunomide medac with food, drink and alcohol
Leflunomide medac may be taken with or without food.
It is not recommended to drink alcohol during treatment with Leflunomide medac. Drinking alcohol while taking Leflunomide medac may increase the chance of liver damage.

Pregnancy and breast-feeding
Do not take Leflunomide medac if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking Leflunomide medac, the risk of having a baby with serious birth defects is increased. Women of childbearing potential must not take Leflunomide medac without using reliable contraceptive measures.

Tell your doctor if you plan to become pregnant after stopping treatment with Leflunomide medac, as you need to ensure that all traces of Leflunomide medac have left your body before trying to become pregnant. This may take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of Leflunomide medac from your body.
In either case it should be confirmed by a blood test that Leflunomide medac has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking Leflunomide medac or in the two years after you have stopped treatment, you must contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove Leflunomide medac rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Do not take Leflunomide medac when you are **breast-feeding**, as leflunomide passes into the breast milk.

Driving and using machines
Leflunomide medac can make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

Leflunomide medac contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Leflunomide medac contains soya lecithin.
If you are allergic to peanut or soya, do not use this medicine.

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

3. How to take Leflunomide medac

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual starting dose of Leflunomide medac is 100 mg once daily for the first three days. After this, most patients need a dose of:
- For rheumatoid arthritis: 10 to 20 mg Leflunomide medac once daily, depending on the severity of the disease.
- For psoriatic arthritis: 20 mg Leflunomide medac once daily.

Swallow the tablet **whole** and with plenty of **water**.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.
You will normally take Leflunomide medac over long periods of time.

If you take more Leflunomide medac than you should
If you take more Leflunomide medac than you should, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Leflunomide medac
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** and stop taking Leflunomide medac:
- if you experience **weakness**, feel light-headed or dizzy or have **difficulty breathing,** as these may be signs of a serious allergic reaction,
- if you develop a **skin rash** or **ulcers in your mouth**, as these may indicate severe, sometimes life-threatening reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), see section 2.

Tell your doctor **immediately** if you experience:
- **pale skin**, **tiredness,** or **bruising,** as these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood,
- **tiredness**, **abdominal pain**, or **jaundice** (yellow discolouration of the eyes or skin), as these may indicate serious conditions such as liver failure, which may be fatal,

- any symptoms of an **infection** such as **fever, sore throat** or **cough,** as this medicine may increase the chance of a severe infection which may be life-threatening,
- **cough** or **breathing problems** as these may indicate problems of the lung (interstitial lung disease, pulmonary hypertension or pulmonary nodule),
- unusual tingling, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy).

Common side effects (may affect up to 1 in 10 people)
- a slight decrease in the number of white blood cells (leucopenia),
- mild allergic reactions,
- loss of appetite, weight loss (usually insignificant),
- tiredness (asthenia),
- headache, dizziness,
- abnormal skin sensations like tingling (paraesthesia),
- mild increase in blood pressure,
- colitis,
- diarrhoea,
- nausea, vomiting,
- inflammation of the mouth or mouth ulcers,
- abdominal pain,
- an increase in some liver test results,
- increased hair loss,
- eczema, dry skin, rash, itching,
- tendonitis (pain caused by inflammation in the membrane surrounding the tendons usually in the feet or hands),
- an increase of certain enzymes in the blood (creatine phosphokinase),
- problems in the nerves of the arms or legs (peripheral neuropathy).

Uncommon side effects (may affect up to 1 in 100 people)
- a decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia),
- a decrease in the levels of potassium in the blood,
- anxiety,
- taste disturbances,
- urticaria (nettle rash),
- tendon rupture,
- an increase in the levels of fat in the blood (cholesterol and triglycerides),
- a decrease in the levels of phosphate in the blood.

Rare side effects (may affect up to 1 in 1,000 people)
- an increase in the numbers of blood cells called eosinophiles (eosinophilia); mild decrease in the number of white blood cells (leucopenia); decrease in the number of all blood cells (pancytopenia),
- severe increase in blood pressure,
- inflammation of the lung (interstitial lung disease),
- an increase in some liver results which may develop into serious conditions such as hepatitis and jaundice,
- severe infections called sepsis which may be fatal,
- an increase of certain enzymes in the blood (lactate dehydrogenase).

Very rare side effects (may affect up to 1 in 10,000 people)
- a marked decrease of some white blood cells (agranulocytosis),
- severe and potentially severe allergic reactions,
- inflammation of blood vessels (vasculitis, including cutaneous necrotizing vasculitis),
- inflammation of the pancreas (pancreatitis),
- severe liver injury such as liver failure or necrosis which may be fatal,

- severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, pulmonary hypertension, male infertility (which is reversible once treatment with this medicine is stopped), cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light), psoriasis (new or worsening), DRESS and skin ulcer (round, open sore in the skin through which the underlying tissues can be seen) may also occur with an unknown frequency.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Leflunomide medac

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the bottle after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Leflunomide medac contains

- The active substance is leflunomide.
  One tablet of Leflunomide medac 10 mg film-coated tablets contains 10 mg of leflunomide.
- The other ingredients are lactose monohydrate, low-substituted hydroxypropyl cellulose, tartaric acid, sodium laurylsulfate and magnesium stearate in the tablet core as well as lecithin (soybeans), poly(vinyl alcohol), talc, titanium dioxide (E 171) and xanthan gum in the film-coating.

What Leflunomide medac looks like and contents of the pack

Leflunomide medac 10 mg film-coated tablets are white to almost white and round with a diameter of about 6 mm.

The tablets are packed in bottles.
Leflunomide medac 10 mg film-coated tablets: Pack sizes of 30, 60 or 100 film-coated tablets per bottle are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

Manufacturer

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Pharmanovia Benelux B.V.
Tél/Tel: +31 76 560 0030
Leflunomide@medac.eu

Κύπρος
Gidamed Medical Supplies Ltd.
Τηλ:+ 357-257 510 30
Leflunomide@medac.eu

България
medac GmbH
Тел.:+49 4103 8006-0
Leflunomide@medac.eu

Luxembourg/Luxemburg
medac GmbH
Tél/Tel: +49 4103 8006-0
Leflunomide@medac.eu

Česká republika / Slovenská republika
medac GmbH organizacni slozka
Tel: +420 774 486 166
Leflunomid@medac.eu

Magyarország
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Danmark / Sverige
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf.: +46 44 7850 666
Leflunomide@medac.eu

Malta
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Deutschland
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Nederland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Eesti / Latvija / Lietuva
ViaSana
Tel: +370 5 2788 414
Leflunomide@medac.eu

Ελλάδα
medac GmbH
Τηλ: + 49 4103 8006-0
Leflunomide@medac.eu

España
Laboratorios Gebro Pharma, S.A.
Tel: +34 93 205 86 86
Leflunomida@medac.eu

France
medac s.a.s.
Tél: + 33 437 66 14 70
Leflunomide@medac.eu

Hrvatska
Medis Adria d.o.o.
Tel: + 385 (0) 1 230 34 46
Leflunomid@medac.eu

Ireland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Ísland
Vistor ehf.
Sími: + 354 535 7000
Leflunomide@medac.eu

Italia
medac Pharma S.r.l.
Tel: + 39 06 515912 1
Leflunomide@medac.eu

Norge
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf: + 47 90 63 81 04
Leflunomide@medac.eu

Österreich
EVER Valinject GmbH
Tel: +43 7665 20555
Leflunomide@medac.eu

Polska
medac GmbH Sp. Z.o.o.
Tel: + 48 22 430 00 30
Leflunomid@medac.eu

Portugal
medac–GmbH - Sucursal em Portugal
Tel: + 351 21 410 75 83
Leflunomida@medac.eu

România
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Slovenija
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Suomi/Finland
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Puh/Tel: +358 10 420 4000
Leflunomide@medac.eu

This leaflet was last revised in {MM/YYYY}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

Package leaflet: Information for the user

Leflunomide medac 15 mg film-coated tablets
leflunomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Leflunomide medac is and what it is used for

Leflunomide medac belongs to a group of medicines called anti-rheumatic medicines. It contains the active substance leflunomide.

Leflunomide medac is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis.

Symptoms of rheumatoid arthritis include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (lack of red blood cells).

Symptoms of active psoriatic arthritis include inflammation of joints, swelling, difficulty in moving, pain, and patches of red, scaly skin (skin lesions).

2. What you need to know before you take Leflunomide medac

Do not take Leflunomide medac
- if you have ever had an **allergic** reaction to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome), peanut or soya or to any of the other ingredients of this medicine (listed in section 6), or if you are allergic to teriflunomide (used to treat multiple sclerosis),
- if you have any **liver problems**,
- if you have moderate to severe **kidney problems**,
- if you have severely low numbers of **proteins in your blood** (hypoproteinaemia),
- if you suffer from any problem which affects your **immune system** (e.g. AIDS),
- if you have any problem with your **bone marrow,** or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets,
- if you are suffering from a **serious infection**,
- if you are **pregnant**, think you may be pregnant, or are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Leflunomide medac
- if you have ever suffered from **inflammation of the lung** (interstitial lung disease**)**,
- if you have ever had **tuberculosis** or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis
- if you are **male** and wish to father a child. As it cannot be excluded that Leflunomide medac passes into semen, reliable contraception should be used during treatment with Leflunomide medac. Men wishing to father a child should contact their doctor who may advise them to stop taking Leflunomide medac and take certain medicines to remove Leflunomide medac rapidly and sufficiently from their body. You will then need a blood test to make sure that Leflunomide medac has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.
- if you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.
- if you will have or have had recent major surgery, or if you still have an unhealed wound following surgery. Leflunomide medac may impair wound healing.

Leflunomide medac can occasionally cause some problems with your blood, liver, lungs or nerves in your arms or legs. It may also cause some serious allergic reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), or increase the chance of a severe infection. For more information on these, please read section 4 (Possible side effects).

DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

Your doctor will carry out **blood tests** at regular intervals, before and during treatment with Leflunomide medac, to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as Leflunomide medac can cause an increase in blood pressure.

Tell your doctor if you have unexplained chronic diarrhoea. Your doctor may perform additional tests for differential diagnosis.

Tell your doctor if you develop skin ulcer during treatment with Leflunomide medac (see also section 4).

Children and adolescents
Leflunomide medac is not recommended for use in children and adolescents below 18 years of age.

Other medicines and Leflunomide medac
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

This is especially important if you are taking:
- other medicines for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate) as these combinations are not advisable,
- warfarin and other oral medicines used to thin the blood, as monitoring is necessary to reduce the risk of side effects of this medicine
- teriflunomide for multiple sclerosis
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhoea
- theophylline for asthma

- tizanidine, a muscle relaxant
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indomethacin, ketoprofen for pain or inflammation
- furosemide for heart disease (diuretic, water pill)
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
  sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- a medicine called colestyramine (used to reduce high cholesterol) or activated charcoal as these medicines can reduce the amount of Leflunomide medac which is absorbed by the body.

If you are already taking a non-steroidal **anti-inflammatory** drug (NSAID) and/or **corticosteroids**, you may continue to take them after starting Leflunomide medac.

Vaccinations
If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking Leflunomide medac, and for a certain amount of time after stopping treatment.

Leflunomide medac with food, drink and alcohol
Leflunomide medac may be taken with or without food.
It is not recommended to drink alcohol during treatment with Leflunomide medac. Drinking alcohol while taking Leflunomide medac may increase the chance of liver damage.

Pregnancy and breast-feeding
Do not take Leflunomide medac if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking Leflunomide medac, the risk of having a baby with serious birth defects is increased. Women of childbearing potential must not take Leflunomide medac without using reliable contraceptive measures.

Tell your doctor if you plan to become pregnant after stopping treatment with Leflunomide medac, as you need to ensure that all traces of Leflunomide medac have left your body before trying to become pregnant. This may take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of Leflunomide medac from your body.
In either case it should be confirmed by a blood test that Leflunomide medac has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking Leflunomide medac or in the two years after you have stopped treatment, you must contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove Leflunomide medac rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Do not take Leflunomide medac when you are **breast-feeding**, as leflunomide passes into the breast milk.

Driving and using machines
Leflunomide medac can make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

Leflunomide medac contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Leflunomide medac contains soya lecithin
If you are allergic to peanut or soya, do not use this medicine.

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

3. How to take Leflunomide medac

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual starting dose of Leflunomide medac is 100 mg once daily for the first three days. After this, most patients need a dose of:
- For rheumatoid arthritis: 10 to 20 mg Leflunomide medac once daily, depending on the severity of the disease.
- For psoriatic arthritis: 20 mg Leflunomide medac once daily.

Swallow the tablet **whole** and with plenty of **water**.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.
You will normally take Leflunomide medac over long periods of time.

If you take more Leflunomide medac than you should
If you take more Leflunomide medac than you should, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Leflunomide medac
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** and stop taking Leflunomide medac:
- if you experience **weakness**, feel light-headed or dizzy or have **difficulty breathing,** as these may be signs of a serious allergic reaction,
- if you develop a **skin rash** or **ulcers in your mouth**, as these may indicate severe, sometimes life-threatening reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), see section 2.

Tell your doctor **immediately** if you experience:
- **pale skin**, **tiredness,** or **bruising,** as these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood,
- **tiredness**, **abdominal pain**, or **jaundice** (yellow discolouration of the eyes or skin), as these may indicate serious conditions such as liver failure, which may be fatal,
- any symptoms of an **infection** such as **fever, sore throat** or **cough,** as this medicine may increase the chance of a severe infection which may be life-threatening,
- **cough** or **breathing problems** as these may indicate problems of the lung (interstitial lung disease, pulmonary hypertension or pulmonary nodule),

- unusual tingling, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy).

Common side effects (may affect up to 1 in 10 people)
- a slight decrease in the number of white blood cells (leucopenia),
- mild allergic reactions,
- loss of appetite, weight loss (usually insignificant),
- tiredness (asthenia),
- headache, dizziness,
- abnormal skin sensations like tingling (paraesthesia),
- mild increase in blood pressure,
- colitis,
- diarrhoea,
- nausea, vomiting,
- inflammation of the mouth or mouth ulcers,
- abdominal pain,
- an increase in some liver test results,
- increased hair loss,
- eczema, dry skin, rash, itching,
- tendonitis (pain caused by inflammation in the membrane surrounding the tendons usually in the feet or hands),
- an increase of certain enzymes in the blood (creatine phosphokinase),
- problems in the nerves of the arms or legs (peripheral neuropathy).

Uncommon side effects (may affect up to 1 in 100 people)
- a decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia),
- a decrease in the levels of potassium in the blood,
- anxiety,
- taste disturbances,
- urticaria (nettle rash),
- tendon rupture,
- an increase in the levels of fat in the blood (cholesterol and triglycerides),
- a decrease in the levels of phosphate in the blood.

Rare side effects (may affect up to 1 in 1,000 people)
- an increase in the numbers of blood cells called eosinophiles (eosinophilia); mild decrease in the number of white blood cells (leucopenia); decrease in the number of all blood cells (pancytopenia),
- severe increase in blood pressure,
- inflammation of the lung (interstitial lung disease),
- an increase in some liver results which may develop into serious conditions such as hepatitis and jaundice,
- severe infections called sepsis which may be fatal,
- an increase of certain enzymes in the blood (lactate dehydrogenase).

Very rare side effects (may affect up to 1 in 10,000 people)
- a marked decrease of some white blood cells (agranulocytosis),
- severe and potentially severe allergic reactions,
- inflammation of blood vessels (vasculitis, including cutaneous necrotizing vasculitis),
- inflammation of the pancreas (pancreatitis),
- severe liver injury such as liver failure or necrosis which may be fatal,
- severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, pulmonary

hypertension, male infertility (which is reversible once treatment with this medicine is stopped), cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light), psoriasis (new or worsening), DRESS and skin ulcer (round, open sore in the skin through which the underlying tissues can be seen) may also occur with an unknown frequency.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Leflunomide medac

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the bottle after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Leflunomide medac contains

- The active substance is leflunomide.
  One tablet of Leflunomide medac 15 mg film-coated tablets contains 15 mg of leflunomide.
- The other ingredients are lactose monohydrate, low-substituted hydroxypropyl cellulose, tartaric acid, sodium laurylsulfate and magnesium stearate in the tablet core as well as lecithin (soybeans), poly(vinyl alcohol), talc, titanium dioxide (E 171) and xanthan gum in the film-coating.

What Leflunomide medac looks like and contents of the pack

Leflunomide medac 15 mg film-coated tablets are white to almost white and round with a diameter of about 7 mm. One side of the tablet is debossed with “15”.

The tablets are packed in bottles.
Leflunomide medac 15 mg film-coated tablets: Pack sizes of 30, 60, 90 or 100 film-coated tablets per bottle are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

Manufacturer

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Pharmanovi a B.V.
Tél/Tel: +31 76 560 0030
Leflunomide@medac.eu

България
medac GmbH
Тел.:+49 4103 8006-0
Leflunomide@medac.eu

Česká republika / Slovenská republika
medac GmbH organizacni slozka
Tel: +420 774 486 166
Leflunomid@medac.eu

Danmark / Sverige
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf.: +46 44 7850 666
Leflunomide@medac.eu

Deutschland
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Eesti / Latvija / Lietuva
ViaSana
Tel: +370 5 2788 414
Leflunomide@medac.eu

Ελλάδα
medac GmbH
Τηλ: + 49 4103 8006-0
Leflunomide@medac.eu

Κύπρος
Gidamed Medical Supplies Ltd.
Τηλ:+ 357-257 510 30
Leflunomide@medac.eu

Luxembourg/Luxemburg
medac GmbH
Tél/Tel: +49 4103 8006-0
Leflunomide@medac.eu

Magyarország
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Malta
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Nederland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Norge
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf: + 47 90 63 81 04
Leflunomide@medac.eu

Österreich
EVER Valinject GmbH
Tel: +43 7665 20555
Leflunomide@medac.eu

España
Laboratorios Gebro Pharma, S.A.
Tel: +34 93 205 86 86
Leflunomida@medac.eu

France
medac s.a.s.
Tél: + 33 437 66 14 70
Leflunomide@medac.eu

Hrvatska
Medis Adria d.o.o.
Tel: + 385 (0) 1 230 34 46
Leflunomid@medac.eu

Ireland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Ísland
Vistor ehf.
Sími: + 354 535 7000
Leflunomide@medac.eu

Italia
medac Pharma S.r.l.
Tel: + 39 06 515912 1
Leflunomide@medac.eu

Polska
medac GmbH Sp. z.o.o.
Tel: + 48 22 430 00 30
Leflunomid@medac.eu

Portugal
medac GmbH - Sucursal em Portugal
Tel: + 351 21 410 75 83
Leflunomida@medac.eu

România
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Slovenija
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Suomi/Finland
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Puh/Tel: +358 10 420 4000
Leflunomide@medac.eu

This leaflet was last revised in {MM/YYYY}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.

Package leaflet: Information for the user

Leflunomide medac 20 mg film-coated tablets
leflunomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Leflunomide medac is and what it is used for

Leflunomide medac belongs to a group of medicines called anti-rheumatic medicines. It contains the active substance leflunomide.

Leflunomide medac is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis.

Symptoms of rheumatoid arthritis include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (lack of red blood cells).

Symptoms of active psoriatic arthritis include inflammation of joints, swelling, difficulty in moving, pain, and patches of red, scaly skin (skin lesions).

2. What you need to know before you take Leflunomide medac

Do not take Leflunomide medac
- if you have ever had an **allergic** reaction to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome), peanut or soya or to any of the other ingredients of this medicine (listed in section 6), or if you are allergic to teriflunomide (used to treat multiple sclerosis),
- if you have any **liver problems**,
- if you have moderate to severe **kidney problems**,
- if you have severely low numbers of **proteins in your blood** (hypoproteinaemia),
- if you suffer from any problem which affects your **immune system** (e.g. AIDS),
- if you have any problem with your **bone marrow,** or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets,
- if you are suffering from a **serious infection**,
- if you are **pregnant**, think you may be pregnant, or are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Leflunomide medac
- if you have ever suffered from **inflammation of the lung** (interstitial lung disease**)**,
- if you have ever had **tuberculosis** or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis
- if you are **male** and wish to father a child. As it cannot be excluded that Leflunomide medac passes into semen, reliable contraception should be used during treatment with Leflunomide medac. Men wishing to father a child should contact their doctor who may advise them to stop taking Leflunomide medac and take certain medicines to remove Leflunomide medac rapidly and sufficiently from their body. You will then need a blood test to make sure that Leflunomide medac has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.
- if you are due to have a specific blood test (calcium level). Falsely low levels of calcium can be detected.
- if you will have or have had recent major surgery, or if you still have an unhealed wound following surgery. Leflunomide medac may impair wound healing.

Leflunomide medac can occasionally cause some problems with your blood, liver, lungs or nerves in your arms or legs. It may also cause some serious allergic reactions (including Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), or increase the chance of a severe infection. For more information on these, please read section 4 (Possible side effects).

DRESS appears initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.

Your doctor will carry out **blood tests** at regular intervals, before and during treatment with Leflunomide medac, to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as Leflunomide medac can cause an increase in blood pressure.

Tell your doctor if you have unexplained chronic diarrhoea. Your doctor may perform additional tests for differential diagnosis.

Tell your doctor if you develop skin ulcer during treatment with Leflunomide medac (see also section 4).

Children and adolescents
Leflunomide medac is not recommended for use in children and adolescents below 18 years of age.

Other medicines and Leflunomide medac
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

This is especially important if you are taking:
- other medicines for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate) as these combinations are not advisable,
- warfarin and other oral medicines used to thin the blood, as monitoring is necessary to reduce the risk of side effects of this medicine
- teriflunomide for multiple sclerosis
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhoea

- theophylline for asthma
- tizanidine, a muscle relaxant
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indomethacin, ketoprofen for pain or inflammation
- furosemide for heart disease (diuretic, water pill)
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- a medicine called colestyramine (used to reduce high cholesterol) or activated charcoal as these medicines can reduce the amount of Leflunomide medac which is absorbed by the body.

If you are already taking a non-steroidal **anti-inflammatory** drug (NSAID) and/or **corticosteroids**, you may continue to take them after starting Leflunomide medac.

Vaccinations
If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking Leflunomide medac, and for a certain amount of time after stopping treatment.

Leflunomide medac with food, drink and alcohol
Leflunomide medac may be taken with or without food.
It is not recommended to drink alcohol during treatment with Leflunomide medac. Drinking alcohol while taking Leflunomide medac may increase the chance of liver damage.

Pregnancy and breast-feeding
Do not take Leflunomide medac if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking Leflunomide medac, the risk of having a baby with serious birth defects is increased. Women of childbearing potential must not take Leflunomide medac without using reliable contraceptive measures.

Tell your doctor if you plan to become pregnant after stopping treatment with Leflunomide medac, as you need to ensure that all traces of Leflunomide medac have left your body before trying to become pregnant. This may take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of Leflunomide medac from your body.
In either case it should be confirmed by a blood test that Leflunomide medac has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking Leflunomide medac or in the two years after you have stopped treatment, you must contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove Leflunomide medac rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Do not take Leflunomide medac when you are **breast-feeding**, as leflunomide passes into the breast milk.

Driving and using machines
Leflunomide medac can make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

Leflunomide medac contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Leflunomide medac contains soya lecithin
If you are allergic to peanut or soya, do not use this medicine.

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

3. How to take Leflunomide medac

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual starting dose of Leflunomide medac is 100 mg once daily for the first three days. After this, most patients need a dose of:
- For rheumatoid arthritis: 10 to 20 mg Leflunomide medac once daily, depending on the severity of the disease.
- For psoriatic arthritis: 20 mg Leflunomide medac once daily.

Swallow the tablet **whole** and with plenty of **water**.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.
You will normally take Leflunomide medac over long periods of time.

If you take more Leflunomide medac than you should
If you take more Leflunomide medac than you should, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

If you forget to take Leflunomide medac
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** and stop taking Leflunomide medac:
- if you experience **weakness**, feel light-headed or dizzy or have **difficulty breathing,** as these may be signs of a serious allergic reaction,
- if you develop a **skin rash** or **ulcers in your mouth**, as these may indicate severe, sometimes life-threatening reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), see section 2.

Tell your doctor **immediately** if you experience:

- **pale skin**, **tiredness,** or **bruising,** as these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood,
- **tiredness**, **abdominal pain**, or **jaundice** (yellow discolouration of the eyes or skin), as these may indicate serious conditions such as liver failure, which may be fatal,
- any symptoms of an **infection** such as **fever, sore throat** or **cough,** as this medicine may increase the chance of a severe infection which may be life-threatening,
- **cough** or **breathing problems** as these may indicate problems of the lung (interstitial lung disease, pulmonary hypertension or pulmonary nodule),
- unusual tingling, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy).

Common side effects (may affect up to 1 in 10 people)

- a slight decrease in the number of white blood cells (leucopenia),
- mild allergic reactions,
- loss of appetite, weight loss (usually insignificant),
- tiredness (asthenia),
- headache, dizziness,
- abnormal skin sensations like tingling (paraesthesia),
- mild increase in blood pressure,
- colitis,
- diarrhoea,
- nausea, vomiting,
- inflammation of the mouth or mouth ulcers,
- abdominal pain,
- an increase in some liver test results,
- increased hair loss,
- eczema, dry skin, rash, itching,
- tendonitis (pain caused by inflammation in the membrane surrounding the tendons usually in the feet or hands),
- an increase of certain enzymes in the blood (creatine phosphokinase),
- problems in the nerves of the arms or legs (peripheral neuropathy).

Uncommon side effects (may affect up to 1 in 100 people)

- a decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia),
- a decrease in the levels of potassium in the blood,
- anxiety,
- taste disturbances,
- urticaria (nettle rash),
- tendon rupture,
- an increase in the levels of fat in the blood (cholesterol and triglycerides),
- a decrease in the levels of phosphate in the blood.

Rare side effects (may affect up to 1 in 1,000 people)

- an increase in the numbers of blood cells called eosinophiles (eosinophilia); mild decrease in the number of white blood cells (leucopenia); decrease in the number of all blood cells (pancytopenia),
- severe increase in blood pressure,
- inflammation of the lung (interstitial lung disease),
- an increase in some liver results which may develop into serious conditions such as hepatitis and jaundice,
- severe infections called sepsis which may be fatal,
- an increase of certain enzymes in the blood (lactate dehydrogenase).

Very rare side effects (may affect up to 1 in 10,000 people)
- a marked decrease of some white blood cells (agranulocytosis),
- severe and potentially severe allergic reactions,
- inflammation of blood vessels (vasculitis, including cutaneous necrotizing vasculitis),
- inflammation of the pancreas (pancreatitis),
- severe liver injury such as liver failure or necrosis which may be fatal,
- severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Other side effects such as kidney failure, a decrease in the levels of uric acid in your blood, pulmonary hypertension, male infertility (which is reversible once treatment with this medicine is stopped), cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light), psoriasis (new or worsening), DRESS and skin ulcer (round, open sore in the skin through which the underlying tissues can be seen) may also occur with an unknown frequency.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Leflunomide medac

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the bottle after EXP. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Leflunomide medac contains

- The active substance is leflunomide.
  One tablet of Leflunomide medac 20 mg film-coated tablets contains 20 mg of leflunomide.
- The other ingredients are lactose monohydrate, low-substituted hydroxypropyl cellulose, tartaric acid, sodium laurylsulfate and magnesium stearate in the tablet core as well as lecithin (soybeans), poly(vinyl alcohol), talc, titanium dioxide (E 171) and xanthan gum in the film-coating.

What Leflunomide medac looks like and contents of the pack

Leflunomide medac 20 mg film-coated tablets are white to almost white and round with a diameter of about 8 mm and a break-mark on one side of the tablet. The tablet can be divided into equal halves.

The tablets are packed in bottles.
Leflunomide medac 20 mg film-coated tablets: Pack sizes of 15, 30, 60 or 100 film-coated tablets per bottle are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

Manufacturer

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Pharmanovia B.V.
Tél/Tel: +31 76 560 0030
Leflunomide@medac.eu

Κύπρος
Gidamed Medical Supplies Ltd.
Τηλ:+ 357-257 510 30
Leflunomide@medac.eu

България
medac GmbH
Тел.:+49 4103 8006-0
Leflunomide@medac.eu

Luxembourg/Luxemburg
medac GmbH
Tél/Tel: +49 4103 8006-0
Leflunomide@medac.eu

Česká republika / Slovenská republika
medac GmbH organizacni slozka
Tel: +420 774 486 166
Leflunomid@medac.eu

Magyarország
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Danmark / Sverige
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf.: +46 44 7850 666
Leflunomide@medac.eu

Malta
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Deutschland
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Nederland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Eesti / Latvija / Lietuva
ViaSana
Tel: +370 5 2788 414
Leflunomide@medac.eu

Ελλάδα
medac GmbH
Τηλ: + 49 4103 8006-0
Leflunomide@medac.eu

España
Laboratorios Gebro Pharma, S.A.
Tel: +34 93 205 86 86
Leflunomida@medac.eu

France
medac s.a.s.
Tél: + 33 437 66 14 70
Leflunomide@medac.eu

Hrvatska
Medis Adria d.o.o.
Tel: + 385 (0) 1 230 34 46
Leflunomid@medac.eu

Ireland
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Ísland
Vistor ehf.
Sími: + 354 535 7000
Leflunomide@medac.eu

Italia
medac Pharma S.r.l.
Tel: + 39 06 515912 1
Leflunomide@medac.eu

Norge
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Tlf: + 47 90 63 81 04
Leflunomide@medac.eu

Österreich
EVER Valinject GmbH
Tel: +43 7665 20555
Leflunomide@medac.eu

Polska
medac GmbH Sp. z.o.o.
Tel: + 48 22 430 00 30
Leflunomid@medac.eu

Portugal
medac GmbH - Sucursal em Portugal
Tel: + 351 21 410 75 83
Leflunomida@medac.eu

România
medac GmbH
Tel: +49 4103 8006-0
Leflunomide@medac.eu

Slovenija
medac GmbH
Tel: +49 4103 8006-0
Leflunomid@medac.eu

Suomi/Finland
medac
Gesellschaft für klinische
Spezialpräparate G.m.b.H, Tyskland, filial
Puh/Tel: +358 10 420 4000
Leflunomide@medac.eu

This leaflet was last revised in {MM/YYYY}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu.