ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of leflunomide.

Excipients with known effect:
Each tablet contains 97.25 mg of lactose monohydrate and 3.125 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round film-coated tablets, engraved with “10” on one side and “L” on the other.

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).

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.

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.

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 Teva 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 Teva 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 to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) 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 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.

Liver reactions

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. 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 from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and 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 Teva 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 Teva 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.

Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

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 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 Teva 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 contra-indicated (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.

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.

The risk of tuberculosis should be considered. A tuberculin reaction test should be considered for those patients with other tuberculosis risk factors.

Respiratory reactions

Interstitial lung disease has been reported during treatment with leflunomide (see section 4.8). The risk of its occurrence is increased in patients with a history of interstitial lung disease.
Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and 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 Teva. Most patients improved after discontinuation of Leflunomide Teva. 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 Teva develops a peripheral neuropathy, consider discontinuing Leflunomide Teva therapy and performing the drug elimination procedure (see section 4.4).

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.

Lactose

Leflunomide Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 drugs or when leflunomide treatment is followed by such drugs 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.

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 drugs 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 drugs 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.

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.

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

The enzymes involved in the metabolism of leflunomide and its metabolites are not exactly known. An *in vivo* interaction study with cimetidine (non-specific cytochrome P450 inhibitor) has demonstrated a lack of a significant interaction. 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.

In vitro studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. In clinical trials no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

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.

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 Teva.

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 Teva is contraindicated in 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.

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

Gastrointestinal disorders

Common:	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

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

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose, and reports of acute overdose in adults and children. There were no adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: abdominal pain, nausea, 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: L04AA13.

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.

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 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. 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.

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-lifeof 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 drug 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 pediatric 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 pediatric 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
Povidone
Crospovidone type A
Pregelatinized starch (maize)
Talc
Silica, colloidal anhydrous
Lactose anhydrous
Magnesium stearate

Tablet coating:
Titanium dioxide (E171)
Polydextrose (E1200)
Hypromellose (E464)
Triethyl citrate (E1505)
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE containers: 2 years.
Blisters: 2 years.

6.4 Special precautions for storage

HDPE containers: Do not store above 30°C.
Blisters: Do not store above 25°C.

6.5 Nature and contents of container

HDPE tablet container with polypropylene screw cap. Pack sizes of 30 and 100 film-coated tablets.

OPA/Alu/PVC – Aluminium blisters. Pack sizes of 28, 30 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of leflunomide.

Excipients with known effect::
Each tablet contains 194.5 mg of lactose monohydrate and 6.25 mg anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Dark beige, triangle shaped, film-coated tablets, engraved with ”20” on one side and “L” on the other.

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).

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.

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.

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 Teva 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 Teva 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 to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) 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 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.

Liver reactions

Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. 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 from 20 mg to 10 mg may be considered and monitoring must be performed weekly. If ALT (SGPT) elevations of more than 2-fold the upper limit of normal persist or if ALT elevations of more than 3-fold the upper limit of normal are present, leflunomide must be discontinued and 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 Teva 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 Teva 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.

Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

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 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 Teva 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 contra-indicated (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.

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.

The risk of tuberculosis should be considered. A tuberculin reaction test should be considered for those patients with other tuberculosis risk factors.

Respiratory reactions

Interstitial lung disease has been reported during treatment with leflunomide (see section 4.8). The risk of its occurrence is increased in patients with a history of interstitial lung disease.
Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Pulmonary symptoms, such as cough and 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 Teva. Most patients improved after discontinuation of Leflunomide Teva. 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 Teva develops a peripheral neuropathy, consider discontinuing Leflunomide Teva therapy and performing the drug elimination procedure (see section 4.4).

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.

Lactose

Leflunomide Teva contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 drugs or when leflunomide treatment is followed by such drugs 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.

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 drugs 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 drugs 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.

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.

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

The enzymes involved in the metabolism of leflunomide and its metabolites are not exactly known. An *in vivo* interaction study with cimetidine (non-specific cytochrome P450 inhibitor) has demonstrated a lack of a significant interaction. 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.

In vitro studies indicate that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. In clinical trials no safety problems were observed when leflunomide and NSAIDs metabolised by CYP2C9 were co-administered. Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

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.

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 Teva.

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 Teva is contraindicated in 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.

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

Gastrointestinal disorders

Common:	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

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

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking leflunomide at daily doses up to five times the recommended daily dose, and reports of acute overdose in adults and children. There were no adverse events reported in the majority of case reports of overdose. Adverse events consistent with the safety profile for leflunomide were: abdominal pain, nausea, 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: L04AA13.

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.

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 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. 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.

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-lifeof 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 drug 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 pediatric 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 pediatric 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
Povidone
Crospovidone type A
Pregelatinized starch (maize)
Talc
Silica, colloidal anhydrous
Lactose anhydrous
Magnesium stearate

Tablet coating:
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400
Iron Oxide Yellow (E172)
Polysorbate (E433)
Quinoline Yellow Aluminium lake (E104)
Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE containers: 2 years.
Blisters: 18 months.

6.4 Special precautions for storage

HDPE containers: Do not store above 30°C.
Blisters: Do not store above 25°C.

6.5 Nature and contents of container

HDPE tablet container with polypropylene screw cap. Pack sizes of 30 and 100 film-coated tablets.

OPA/Alu/PVC – Aluminium blisters. Pack sizes of 28, 30 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/006-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13
4042 Debrecen
Hungary

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, East Sussex,
BN22 9AG
United Kingdom

TEVA Santé
Rue Bellocier
89107 Sens
France

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).

The Marketing Authorisation Holder (MAH) shall ensure that any changes to the safety profile of the reference medicinal product requiring changes to the Risk Management Plan or Product Information are immediately implemented for Leflunomide Teva.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs
The PSUR cycle of Leflunomide Teva will correspond to the one attributed to the reference medicinal product, Arava, until otherwise specified.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Leflunomide Teva 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 CARTON/BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 10 mg film-coated tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of leflunomide

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablets whole.
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

Do not store above 25°C

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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/003 28 film-coated tablets
EU/1/11/675/004 30 film-coated tablets
EU/1/11/675/005 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Leflunomide Teva 10 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 10 mg film-coated tablets
leflunomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 10 mg film-coated tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg of leflunomide

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablets whole.
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

Do not store above 30°C

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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/001 30 film-coated tablets
EU/1/11/675/002 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Leflunomide Teva 10 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 10 mg tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of leflunomide

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

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

Teva Pharma B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/001 30 film-coated tablets
EU/1/11/675/002 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 20 mg film-coated tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of leflunomide

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablets whole.
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

Do not store above 25°C

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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/008 28 film-coated tablets
EU/1/11/675/009 30 film-coated tablets
EU/1/11/675/010 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Leflunomide Teva 20 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 20 mg film-coated tablets
leflunomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/BOTTLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 20 mg film-coated tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg of leflunomide

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow tablets whole.
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

Do not store above 30°C

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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/006 30 film-coated tablets
EU/1/11/675/007 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Leflunomide Teva 20 mg film-coated tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Leflunomide Teva 20 mg tablets
leflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg of leflunomide

3. LIST OF EXCIPIENTS

Contains lactose (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

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

Teva Pharma B.V.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/675/006 30 film-coated tablets
EU/1/11/675/007 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Leflunomide Teva 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.

What is in this leaflet

1. What Leflunoamide Teva is and what it is used for

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

Leflunomide Teva is used to treat adult patients with active rheumatoid arthritis.

Rheumatoid arthritis is a crippling form of arthritis. The symptoms 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 anemia (lack of red blood cells).

2. What you need to know before you take Leflunoamide Teva

Do not take Leflunomide Teva
- If you are **allergic** to leflunomide (especially a serious skin reaction, often with fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome) or any of the other ingredients of this medicine (listed in section 6).
- If you have **liver problems**.
- If you suffer from a severe condition that affects your **immune system** e.g. AIDS.
- If you have **bone marrow problems**, or if you have low numbers of red or white blood cells or a reduced number of blood platelets, due to causes other than rheumatoid or psoriatic arthritis.
- If you have a **serious infection**.
- If you suffer from **moderate to severe kidney problems**.
- If you have **very low levels of protein in your blood** (hypoproteinaemia).
- 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 Teva

- If you already have **low red or white blood cells** (anaemia or leucopenia), **low blood platelets**, which may increase your bleeding or bruising (thrombocytopenia), **low bone marrow function** or if you are at risk of your bone marrow not working properly your doctor may advise you to take certain medicines to speed up the removal of Leflunomide Teva from your body.
- If you develop **swollen spongy gums**, **ulcers**, and **loose teeth** (an infectious mouth disease known as ulcerative stomatitis) then you should contact your doctor who may advise you to stop taking Leflunomide Teva.
- If you **switch to another medicine** to treat your rheumatoid arthritis or if you have recently taken medicines that may be harmful to your liver or blood, your doctor may advise you to take certain medicines to speed up the removal of Leflunomide Teva from your body or may closely monitor you when you start taking Leflunomide Teva.
- If you have ever had **tuberculosis** or **interstitial lung disease** (lung disease).
- If you are **male** and wish to father a child. As it cannot be excluded that Leflunomide Teva passes into semen, reliable contraception should be used during treatment with Leflunomide Teva. Men wishing to father a child should contact their doctor who may advise them to stop taking Leflunomide Teva and take certain medicines to remove Leflunomide Teva rapidly and sufficiently from their body. You will then need a blood test to make sure that Leflunomide Teva has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.

Leflunomide Teva 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, or increase the chance of a severe infection. For more information on these, please read section 4 (Possible Side Effects).

Before and during treatment with Leflunomide Teva, your doctor will carry out **blood tests** at regular times. This is to monitor your blood cells and liver. Since Leflunomide Teva can cause an increase in your blood pressure, your doctor will also check your blood pressure regularly.

Children and adolescents

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

Other medicines and Leflunoamide Teva
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially if you are taking any of the following:
- **Any other medicine used to treat rheumatoid arthritis**, e.g. methotrexate and azathioprine (immunosuppressants), chloroquine and hydroxychloroquine (antimalarials), gold (by mouth or injection), and D-penicillamine. Because you may get increased side effects, it is not recommended to take any of these medicines while you are taking Leflunomide Teva.
- **Colestyramine** (used to lower cholesterol levels and treat itching associated with jaundice) or activated charcoal as these medicines can reduce the amount of LeflunomideTeva absorbed by your body.
- Other medicines that are broken down by an enzyme called CYP2C9 e.g. **phenytoin** (an epilepsy treatment), **warfarin** and **phenprocoumon** (blood thinners), and **tolbutamide** (a type 2 diabetes treatment). Discuss with your doctor to find out if any medicine you are taking is broken down by CYP2C9.

If you are already taking **non-steroidal anti-inflammatory drugs** (NSAIDs) and/or **corticosteroids**, you may continue to use these after starting Leflunomide Teva.

Vaccinations
Please discuss with your doctor if you have to take any vaccinations. Some vaccinations should not be given while taking Leflunomide Teva, and for a certain amount of time after stopping treatment.

Leflunomide Teva with food, drink and alcohol
Drinking alcohol while taking Leflunomide Teva may increase the chance of liver damage. Therefore, it is **not recommended** to drink alcohol during treatment.

Pregnancy and breast-feeding
Do not take Leflunomide Teva **if you are pregnant, or think you may be pregnant**. If you are pregnant or become pregnant while taking Leflunomide Teva, the risk of having a baby with serious birth defects is increased.

If you are still able to have a child, **you must not take** Leflunomide Teva **without using reliable contraception for at least 2 years after treatment**. This 2 years may be reduced to a few weeks if you take a treatment, recommended by your doctor, which speeds up removal of Leflunomide Teva from your body.

If you think you **may be pregnant** while you are taking Leflunomide Teva, contact your doctor **immediately** for a pregnancy test. If you are pregnant, your doctor will discuss with you the risks to the pregnancy. Your doctor may recommend a treatment to remove Leflunomide Teva rapidly and sufficiently from your body. This may decrease the risk to your baby.

If after stopping treatment with Leflunomide Teva you **plan to become pregnant**, you need to ensure that Leflunomide Teva has left your body before trying to become pregnant. This should be confirmed by a blood test. If Leflunomide Teva has been sufficiently removed from your body, you should wait at least another 6 weeks before you become pregnant.

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

Leflunomide Teva passes into breast milk. Therefore, **do not breast-feed** during treatment.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Leflunomide Teva may make you dizzy. This may affect your ability to concentrate or react properly. **If this happens to you, do not drive or machines**.

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

3. How to take Leflunomide Teva

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 doctor that starts you on Leflunomide Teva and supervises you while you are on it should be experienced in the treatment of rheumatoid arthritis.

The usual starting dose is 100 mg once a day for 3 days. After this the dose is 10 mg or 20 mg once daily depending on the severity of the disease.

Leflunomide Teva tablets should be **swallowed whole** with plenty of **water**. Leflunomide Teva tablets can be taken with or without food.

It will take 4 to 6 weeks before you feel an improvement in your condition. Some people will notice further improvement after 4 to 6 months of treatment.

You will normally take Leflunomide Teva over long periods of time.

If you take more Leflunomide Teva than you should
If you or someone else swallows a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Leflunomide Teva
In case you forget to take a dose, take it as soon as you remember. 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 Teva:
- If you feel **weak**, 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).

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.
- A **cough** or **breathing problems** as these may indicate inflammation of the lung (interstitial lung disease).
- 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)
- Mild increase in blood pressure.

- Reduction in the number of white blood cells, which makes infections more likely (leucopenia).
- Skin sensation, i.e. burning, prickling, itching, or tingling (paraesthesia).
- Hedache.
- Dizziness.
- Diarrhoea.
- Nausea.
- Vomiting.
- Mouth ulcers or inflammation.
- Abdominal pain.
- Increased hair loss.
- Eczema.
- Rash.
- Itching.
- Dry skin.
- Pain, swelling and tenderness most often in the hand or wrist.
- An increase of certain enzymes in the blood (creatine phosphokinase).
- Loss of appetite.
- Weight loss (usually insignificant).
- Lack or loss of strength (weakness).
- Mild allergic reactions.
- An increase in some liver test results.
- problems in the nerves of the arms or legs (peripheral neuropathy).

Uncommon side effects (may affect up to 1 in 100 people)
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia).
- Mild reduction in blood platelets, which increases the risk of bleeding or bruising.
- Taste disturbances.
- Nettle rash (urticaria).
- Ruptured tendons.
- Low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm.
- An increase in the levels of fat in the blood (cholesterol and triglycerides).
- A decrease in the levels of phosphate in the blood.
- Anxiety.

Rare side effects (may affect up to 1 in 1,000 people)
- Severe increase in blood pressure.
- Severe reduction in blood cells which can cause weakness, bruising or make infections more likely.
- Severe reduction in the number of white blood cells, which makes infections more likely (leucopenia).
- Blood disorder.
- Inflammation of the lung (interstitial lung disease), which may be fatal.
- An increase of lactate dehydrogenase (a blood enzyme).
- Severe infections (including sepsis), which may be fatal.
- Hepatitis (inflammation of the liver).
- Yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice).

Very rare side effects (may affect up to 1 in 10,000 people)
- An infection characterised by high fever, sore throat, skin lesions and an extreme reduction of white blood cells (agranulocytosis).

- Inflammation of the pancreas, which causes severe pain in the abdomen and back.
- Severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).
- Severe allergic reaction.
- Inflammation of the small vessels (vasculitis, including cutaneous necrotizing vasculitis).
- Severe liver damage (i.e. liver failure, liver necrosis), which may be fatal.

Not known side effects (frequency cannot be estimated from the available data):
- Kidney failure.
- Abnormal decrease in the levels of blood uric acid.
- Reversible male infertility.
- Cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light)
- Psoriasis (new or worsening)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Leflunoamide Teva

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

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

For tablets stored in bottles: Do not store above 30°C.
For tablets stored in blisters: Do not store above 25°C.

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 Teva contains

- The active substance is leflunomide.
  - Each Leflunomide Teva 10 mg film-coated tablet contains 10 mg of leflunomide.
- The other ingredients are:
  - Tablet core: lactose monohydrate, povidone, crospovidone type A, pregelatinized starch (maize), talc, anhydrous colloidal silica, lactose anhydrous and magnesium stearate.
  - Tablet coating: titanium dioxide, polydextrose, hypromellose, triethyl citrate and macrogol 8000.

What Leflunomide Teva looks like and contents of the pack
Leflunomide Teva 10 mg film-coated tablets are white, round film-coated tablets, engraved with “10” on one side and “L” on the other.

Leflunomide Teva stored in bottles are available in pack sizes of 30 and 100 film-coated tablets.
Leflunomide Teva stored in blisters are available in pack sizes of 28, 30 and 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

Manufacturers:
Teva Pharmaceutical Works Private Limited Company
Pallagi út 13
Debrecen H-4042
Hungary

TEVA UK Ltd
Brampton Road
Hampden Park
Eastbourne, East Sussex
BN22 9AG UK

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

TEVA Santé
Rue Bellocier
89107 Sens
France

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

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A.
Tel/Tél: +32 3 820 73 73

България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Lietuva
UAB “Sicor Biotech”
Tel: +370 5 266 02 03

Luxembourg/Luxemburg
Teva Pharma Belgium S.A.
Tél/Tel: +32 3 820 73 73

Magyarország
Teva Magyarország Zrt
Tel.: +36 1 288 64 00

Malta
Drugsales Ltd.
Tel: +356 21 419070

Deutschland
Teva GmbH
Tel: (49) 731 402 08

Eesti
Teva Eesti esindus UAB Sicor Biotech
Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

España
Teva Pharma, S.L.U
Tél: +(34) 91 387 32 80

France
Teva Santé
Tél: +(33) 1 55 91 7800

Hrvatska
Pliva Hrvatska d.o.o.
Tel: +385 1 37 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 51 321740

Ísland
ratiopharm Oy Sími: +358 20 180 5900

Italia
Teva Italia S.r.l.
Tel: +(39) 028917981

Κύπρος
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

Latvija
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 784 980

Nederland
Teva Nederland B.V.
Tel: +31 (0) 800 0228400

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1 97 00 7

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +(48) 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos Lda
Tel: (351) 21 476 75 50

România
Teva Pharmaceuticals S.R.L
Tel: +4021 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +(421) 2 5726 7911

Suomi/Finland
ratiopharm Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +(46) 42 12 11 00

United Kingdom
Teva UK Limited
Tel: +(44) 1977 628500

This leaflet was last revised in {MM/YYYY}.

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

Package leaflet: Information for the user

Leflunomide Teva 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.

What is in this leaflet

1. What Leflunoamide Teva is and what it is used for

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

Leflunomide Teva is used to treat adult patients with active rheumatoid arthritis.

Rheumatoid arthritis is a crippling form of arthritis. The symptoms 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 anemia (lack of red blood cells).

2. What you need to know before you take Leflunoamide Teva

Do not take Leflunomide Teva
- If you are **allergic** to leflunomide (especially a serious skin reaction, often with fever, joint pain, red skin stains, or blisters e.g. Stevens-Johnson syndrome) or any of the other ingredients of this medicine (listed in section 6).
- If you have **liver problems**.
- If you suffer from a severe condition that affects your **immune system** e.g. AIDS.
- If you have **bone marrow problems**, or if you have low numbers of red or white blood cells or a reduced number of blood platelets, due to causes other than rheumatoid or psoriatic arthritis.
- If you have a **serious infection**.
- If you suffer from **moderate to severe kidney problems**.
- If you have **very low levels of protein in your blood** (hypoproteinaemia).
- 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 Teva

- If you already have **low red or white blood cells** (anaemia or leucopenia), **low blood platelets**, which may increase your bleeding or bruising (thrombocytopenia), **low bone marrow function** or if you are at risk of your bone marrow not working properly your doctor may advise you to take certain medicines to speed up the removal of Leflunomide Teva from your body.
- If you develop **swollen spongy gums**, **ulcers**, and **loose teeth** (an infectious mouth disease known as ulcerative stomatitis) then you should contact your doctor who may advise you to stop taking Leflunomide Teva.
- If you **switch to another medicine** to treat your rheumatoid arthritis or if you have recently taken medicines that may be harmful to your liver or blood, your doctor may advise you to take certain medicines to speed up the removal of Leflunomide Teva from your body or may closely monitor you when you start taking Leflunomide Teva.
- If you have ever had **tuberculosis** or **interstitial lung disease** (lung disease).
- If you are **male** and wish to father a child. As it cannot be excluded that Leflunomide Teva passes into semen, reliable contraception should be used during treatment with Leflunomide Teva. Men wishing to father a child should contact their doctor who may advise them to stop taking Leflunomide Teva and take certain medicines to remove Leflunomide Teva rapidly and sufficiently from their body. You will then need a blood test to make sure that Leflunomide Teva has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.

Leflunomide Teva 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, or increase the chance of a severe infection. For more information on these, please read section 4 (Possible Side Effects).

Before and during treatment with Leflunomide Teva, your doctor will carry out **blood tests** at regular times. This is to monitor your blood cells and liver. Since Leflunomide Teva can cause an increase in your blood pressure, your doctor will also check your blood pressure regularly.

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

Other medicines and Leflunoamide Teva
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially if you are taking any of the following:

- **Any other medicine used to treat rheumatoid arthritis**, e.g. methotrexate and azathioprine (immunosuppressants), chloroquine and hydroxychloroquine (antimalarials), gold (by mouth or injection), and D-penicillamine. Because you may get increased side effects, it is not recommended to take any of these medicines while you are taking Leflunomide Teva.
- **Colestyramine** (used to lower cholesterol levels and treat itching associated with jaundice) or activated charcoal as these medicines can reduce the amount of LeflunomideTeva absorbed by your body.
- Other medicines that are broken down by an enzyme called CYP2C9 e.g. **phenytoin** (an epilepsy treatment), **warfarin** and **phenprocoumon** (blood thinners), and **tolbutamide** (a type 2 diabetes treatment). Discuss with your doctor to find out if any medicine you are taking is broken down by CYP2C9.

If you are already taking **non-steroidal anti-inflammatory drugs** (NSAIDs) and/or **corticosteroids**, you may continue to use these after starting Leflunomide Teva.

Vaccinations
Please discuss with your doctor if you have to take any vaccinations. Some vaccinations should not be given while taking Leflunomide Teva, and for a certain amount of time after stopping treatment.

Leflunomide Teva with food, drink and alcohol
Drinking alcohol while taking Leflunomide Teva may increase the chance of liver damage. Therefore, it is **not recommended** to drink alcohol during treatment.

Pregnancy and breast-feeding
Do not take Leflunomide Teva **if you are pregnant, or think you may be pregnant**. If you are pregnant or become pregnant while taking Leflunomide Teva, the risk of having a baby with serious birth defects is increased.

If you are still able to have a child, **you must not take** Leflunomide Teva **without using reliable contraception for at least 2 years after treatment**. This 2 years may be reduced to a few weeks if you take a treatment, recommended by your doctor, which speeds up removal of Leflunomide Teva from your body.

If you think you **may be pregnant** while you are taking Leflunomide Teva, contact your doctor **immediately** for a pregnancy test. If you are pregnant, your doctor will discuss with you the risks to the pregnancy. Your doctor may recommend a treatment to remove Leflunomide Teva rapidly and sufficiently from your body. This may decrease the risk to your baby.

If after stopping treatment with Leflunomide Teva you **plan to become pregnant**, you need to ensure that Leflunomide Teva has left your body before trying to become pregnant. This should be confirmed by a blood test. If Leflunomide Teva has been sufficiently removed from your body, you should wait at least another 6 weeks before you become pregnant.

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

Leflunomide Teva passes into breast milk. Therefore, **do not breast-feed** during treatment.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Leflunomide Teva may make you dizzy. This may affect your ability to concentrate or react properly. **If this happens to you, do not drive or machines**.

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

3. How to take Leflunoamide Teva

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 doctor that starts you on Leflunomide Teva and supervises you while you are on it should be experienced in the treatment of rheumatoid arthritis.

The usual starting dose is 100 mg once a day for 3 days. After this the dose is 10 mg or 20 mg once daily depending on the severity of the disease.

Leflunomide Teva tablets should be **swallowed whole** with plenty of **water**. Leflunomide Teva tablets can be taken with or without food.

It will take 4 to 6 weeks before you feel an improvement in your condition. Some people will notice further improvement after 4 to 6 months of treatment.

You will normally take Leflunomide Teva over long periods of time.

If you take more Leflunomide Teva than you should
If you or someone else swallows a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take Leflunomide Teva
In case you forget to take a dose, take it as soon as you remember. 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 Teva:
- If you feel **weak**, 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).

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.
- A **cough** or **breathing problems** as these may indicate inflammation of the lung (interstitial lung disease).
- 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)
- Mild increase in blood pressure.
- Reduction in the number of white blood cells, which makes infections more likely (leucopenia).
- Skin sensation, i.e. burning, prickling, itching, or tingling (paraesthesia).
- Hedache.

- Dizziness.
- Diarrhoea.
- Nausea.
- Vomiting.
- Mouth ulcers or inflammation.
- Abdominal pain.
- Increased hair loss.
- Eczema.
- Rash.
- Itching.
- Dry skin.
- Pain, swelling and tenderness most often in the hand or wrist.
- An increase of certain enzymes in the blood (creatine phosphokinase).
- Loss of appetite.
- Weight loss (usually insignificant).
- Lack or loss of strength (weakness).
- Mild allergic reactions.
- An increase in some liver test results.
- problems in the nerves of the arms or legs (peripheral neuropathy).

Uncommon side effects (may affect up to 1 in 100 people)
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia).
- Mild reduction in blood platelets, which increases the risk of bleeding or bruising.
- Taste disturbances.
- Nettle rash (urticaria).
- Ruptured tendons.
- Low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm.
- An increase in the levels of fat in the blood (cholesterol and triglycerides).
- A decrease in the levels of phosphate in the blood.
- Anxiety.

Rare side effects (may affect up to 1 in 1,000 people)
- Severe increase in blood pressure.
- Severe reduction in blood cells which can cause weakness, bruising or make infections more likely.
- Severe reduction in the number of white blood cells, which makes infections more likely (leucopenia).
- Blood disorder.
- Inflammation of the lung (interstitial lung disease), which may be fatal.
- An increase of lactate dehydrogenase (a blood enzyme).
- Severe infections (including sepsis), which may be fatal.
- Hepatitis (inflammation of the liver).
- Yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice).

Very rare side effects (may affect up to 1 in 10,000 people)
- An infection characterised by high fever, sore throat, skin lesions and an extreme reduction of white blood cells (agranulocytosis).
- Inflammation of the pancreas, which causes severe pain in the abdomen and back.
- Severe sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

- Severe allergic reaction.
- Inflammation of the small vessels (vasculitis, including cutaneous necrotizing vasculitis).
- Severe liver damage (i.e. liver failure, liver necrosis), which may be fatal.

Not known side effects (frequency cannot be estimated from the available data):
- Kidney failure.
- Abnormal decrease in the levels of blood uric acid.
- Reversible male infertility.
- Cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light).
- Psoriasis (new or worsening)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Leflunoamide Teva

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

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

For tablets stored in bottles: Do not store above 30°C.
For tablets stored in blisters: Do not store above 25°C.

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 Teva contains

- The active substance is leflunomide.
  - Each Leflunomide Teva 20 mg film-coated tablet contains 20 mg of leflunomide.
- The other ingredients are:
  - Tablet core: lactose monohydrate, povidone, crospovidone type A, pregelatinized starch (maize), talc, anhydrous colloidal silica, lactose anhydrous and magnesium stearate.
  - Tablet coating: titanium dioxide, hypromellose, macrogol 400, iron oxide yellow, polysorbate, quinoline yellow aluminium lake and indigo carmine aluminium Lake.

What Leflunomide Teva looks like and contents of the pack
Leflunomide Teva 20 mg film-coated tablets are dark beige, triangle shaped, film-coated tablets, engraved with ”20” on one side and “L” on the other.

Leflunomide Teva stored in bottles are available in pack sizes of 30 and 100 film-coated tablets.
Leflunomide Teva stored in blisters are available in pack sizes of 28, 30 and 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

Manufacturers:
Teva Pharmaceutical Works Private Limited Company
Pallagi út 13
Debrecen H-4042
Hungary

TEVA UK Ltd
Brampton Road
Hampden Park
Eastbourne, East Sussex
BN22 9AG UK

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

TEVA Santé
Rue Bellocier
89107 Sens
France

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

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A.
Tel/Tél: +32 3 820 73 73

България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland
Teva GmbH
Tel: (49) 731 402 08

Lietuva
UAB “Sicor Biotech”
Tel: +370 5 266 02 03

Luxembourg/Luxemburg
Teva Pharma Belgium S.A.
Tél/Tel: +32 3 820 73 73

Magyarország
Teva Magyarország Zrt
Tel.: +36 1 288 64 00

Malta
Drugsales Ltd.
Tel: +356 21 419070

Nederland
Teva Nederland B.V.
Tel: +31 (0) 800 0228400

Eesti
Teva Eesti esindus UAB Sicor Biotech Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

España
Teva Pharma, S.L.U
Tél: +(34) 91 387 32 80

France
Teva Santé
Tél: +(33) 1 55 91 7800

Hrvatska
Pliva Hrvatska d.o.o.
Tel: +385 1 37 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 51 321740

Ísland
ratiopharm Oy Sími: +358 20 180 5900

Italia
Teva Italia S.r.l.
Tel: +(39) 028917981

Κύπρος
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

Latvija
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 784 980

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1 97 00 7

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +(48) 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos Lda
Tel: (351) 21 476 75 50

România
Teva Pharmaceuticals S.R.L
Tel: +4021 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +(421) 2 5726 7911

Suomi/Finland
ratiopharm Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +(46) 42 12 11 00

United Kingdom
Teva UK Limited
Tel: +(44) 1977 628500

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