ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Arava 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of the active ingredient leflunomide.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

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

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

4.2 Posology and method of administration

ALT (SGPT) and a complete blood cell count, includinga differential white blood cell count anda 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 also section 4.4).

Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily and is 20 mg once daily for psoriatic arthritis (see section 5.1).

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

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

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

The product should be prescribed by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Administration

Arava 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

Arava must not be used in patients with hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients in the tablets.

Leflunomide is contraindicated in:

- patients with impairment of liver function,
- patients with severe immunodeficiency states, e.g. AIDS,
- patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis,
- patients with serious infections,
- 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 also section 4.6). Pregnancy must be excluded before start of treatment with leflunomide.

Women must not breast-feed while they are receiving leflunomide. See also section 4.6.

Male patients should be aware of the possible male-mediated foetal toxicity (see also section 4.4). Reliable contraception during treatment with leflunomide should also be guaranteed.

Arava is not recommended for use in patients under 18 years as its safety and efficacy have not been studied in this age group.

4.4 Special warnings and special precautions for use

Arava should be administered to patients only under careful medical supervision.

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 when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide a washout procedure should be performed (see below).

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 medication 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. Arava 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, leucopoenia, 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, Arava and any concomitant myelosuppressive medication 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 (with the exception of methotrexate, see section 4.5) has not been studied up to now. 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 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 drugs (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, Arava and any other possibly associated medication 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).

Infections

It is known that medications 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.
Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

Respiratory reactions

Interstitial Lung disease has been reported during treatment with leflunomide (see section 4.8). 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.

Blood pressure

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

Procreation (recommendations for men)

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 cholestyramine 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

Cholestyramine 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 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 cholestyramine 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 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 Arava.

4.6 Pregnancy and lactation

Pregnancy

The active metabolite of leflunomide, A771726, is teratogenic in rats and rabbits and it may cause foetal harm in humans.

Leflunomide must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and for a certain period of time thereafter (waiting period or abbreviated washout period; see below). Pregnancy must be excluded before start of treatment with leflunomide.

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.

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:

- cholestyramine 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 cholestyramine 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 cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Lactation

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

Classification of expected frequencies:

Common = 1 - 10 % of patients; uncommon = 0.1 - 1 % of patients; rare = 0.01 - 0.1 % of patients; very rare = 0.01 % of patients or less.

Cardiac disorders

Common: mild increase in blood pressure

Rare: severe increase in blood pressure

Gastrointestinal disorders

Common: diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain,

Hepato-biliary disorders

Common: elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)

Rare: hepatitis, jaundice/cholestasis and very rarely, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Very rare: pancreatitis.

Infections and infestations

Very 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).

Metabolism and nutrition disorders

Common: weight loss (usually insignificant)

Uncommon: hypokalaemia

Nervous system disorders

Common: headache, dizziness, asthenia, paraesthesia

Uncommon: taste disturbances, anxiety

Very rare: peripheral neuropathy

Musculoskeletal and connective tissue disorders

Common: tenosynovitis

Uncommon: tendon rupture

Skin and subcutaneous tissue disorders

Common: increased hair loss, eczema, dry skin

Uncommon: urticaria

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Immune system disorders

Common: mild allergic reactions, rash (including maculopapular rash), pruritus

Very rare: severe anaphylactic/anaphylactoid reactions

Respiratory, thoracic and mediastinal disorders

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

Blood and lymphatic system disorders

Common: leukopenia (leukocytes >2 G/l)

Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)

Rare: eosinophilia, leukopenia (leukocytes <2 G/l), pancytopenia (probably by antiproliferative mechanism)

Very rare: agranulocytosis, vasculitis

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

The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Mild hyperlipidaemia may occur. Uric acid levels usually decrease.
Laboratory findings for which a clinical relevance could not be established include small increases in LDH and CK. Mild hypophosphataemia is uncommon.

Marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility cannot be excluded.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. If a severe undesirable effect of leflunomide occurs, or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure described in section 4.4 has to be followed. The procedure may be repeated as clinically necessary. For suspected severe immunological/allergic reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis, a complete washout is essential.

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking Arava 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, cholestyramine or charcoal is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.

Administration of activated charcoal (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 immunosuppressive agents, 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.

Mode of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity

Rheumatoid arthritis

The efficacy of Arava 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.

Psoriatic arthritis

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

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

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 Arava.

Absorption

Excretion data from the ^{14}C study indicated that at least about 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. In multiple dose studies in patients with rheumatoid arthritis, the pharmacokinetic parameters

of A771726 were linear over the dose range of 5 to 25 mg. In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

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

Metabolism

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 cholestyramine 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.

Pharmacokinetics in renal failure

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.

Pharmacokinetics in liver failure

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.

Influence of age

Pharmacokinetics in subjects under 18 years have not been studied. 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, leukopenia, 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: Maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, lactose monohydrate.

Film-Coating: Talc, hypromellose, titanium dioxide, macrogol 8000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister: Store in the original package.

Bottle: Keep the container tightly closed.

6.5 Nature and contents of container

Blister: Aluminium / Aluminium blister. Pack sizes: 30 and 100 tablets.

Bottle: HDPE-wide-necked bottle, 100 ml with screw cap with integrated desiccant container. Pack sizes: 30 and 100 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/118/001-004

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

02.09.1999

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Arava 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of the active ingredient leflunomide.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with :

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- Active psoriatic arthritis.

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

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

4.2 Posology and method of administration

ALT (SGPT) and a complete blood cell count, includinga differential white blood cell count anda 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 also section 4.4).

Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose : for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily and is 20 mg once daily for psoriatic arthritis (see section 5.1).

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

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

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

The product should be prescribed by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

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Administration

Arava 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

Arava must not be used in patients with hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients in the tablets.

Leflunomide is contraindicated in:

- patients with impairment of liver function,
- patients with severe immunodeficiency states, e.g. AIDS,
- patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis,
- patients with serious infections,
- 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 also section 4.6). Pregnancy must be excluded before start of treatment with leflunomide.

Women must not breast-feed while they are receiving leflunomide. See also section 4.6.

Male patients should be aware of the possible male-mediated foetal toxicity (see also section 4.4). Reliable contraception during treatment with leflunomide should also be guaranteed.

Arava is not recommended for use in patients under 18 years as its safety and efficacy have not been studied in this age group.

4.4 Special warnings and special precautions for use

Arava should be administered to patients only under careful medical supervision.

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 when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide a washout procedure should be performed (see below).

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 medication 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. Arava 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 anemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of 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, Arava and any concomitant myelosuppressive medication 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 (with the exception of methotrexate, see section 4.5) has not been studied up to now. 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 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 drugs (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, Arava and any other possibly associated medication 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).

Infections

It is known that medications 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.

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

Respiratory reactions

Interstitial Lung disease has been reported during treatment with leflunomide (see section 4.8). 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.

Blood pressure

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

Procreation (recommendations for men)

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 cholestyramine 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

Cholestyramine 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 cholestyramine 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 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 Arava.

4.6 Pregnancy and lactation

Pregnancy

The active metabolite of leflunomide, A771726, is teratogenic in rats and rabbits and it may cause foetal harm in humans.

Leflunomide must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and for a certain period of time thereafter (waiting period or abbreviated washout period; see below). Pregnancy must be excluded before start of treatment with leflunomide.

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.

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:

- cholestyramine 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 cholestyramine 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 cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Lactation

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

Classification of expected frequencies:

common = 1 - 10 % of patients; uncommon = 0.1 - 1 % of patients; rare = 0.01 - 0.1 % of patients; very rare = 0.01 % of patients or less.

Cardiac disorders

Common: mild increase in blood pressure

Rare: severe increase in blood pressure

Gastrointestinal disorders

Common: diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain,

Hepato-biliary disorders

Common: elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)

Rare: hepatitis, jaundice/cholestasis and very rarely, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Very rare: pancreatitis.

Infections and infestations

Very 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).

Metabolism and nutrition disorders

Common: weight loss (usually insignificant)

Uncommon: hypokalaemia

Nervous system disorders

Common: headache, dizziness, asthenia, paraesthesia

Uncommon: taste disturbances, anxiety

Very rare: peripheral neuropathy

Musculoskeletal and connective tissue disorders

Common: tenosynovitis

Uncommon: tendon rupture

Skin and subcutaneous tissue disorders

Common: increased hair loss, eczema, dry skin

Uncommon: urticaria

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Immune system disorders

Common: mild allergic reactions, rash (including maculopapular rash), pruritus

Very rare: severe anaphylactic/anaphylactoid reactions

Respiratory, thoracic and mediastinal disorders

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

Blood and lymphatic system disorders

Common: leukopenia (leukocytes >2 G/l)

Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)

Rare: eosinophilia, leukopenia (leukocytes <2 G/l), pancytopenia (probably by antiproliferative mechanism)

Very rare: agranulocytosis**,** vasculitis

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

The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Mild hyperlipidaemia may occur. Uric acid levels usually decrease.
Laboratory findings for which a clinical relevance could not be established include small increases in LDH and CK. Mild hypophosphataemia is uncommon.

Marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility cannot be excluded.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. If a severe undesirable effect of leflunomide occurs, or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure described in section 4.4 has to be followed. The procedure may be repeated as clinically necessary. For suspected severe immunological/allergic reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis, a complete washout is essential.

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking Arava 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, cholestyramine or charcoal is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.

Administration of activated charcoal (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 immunosuppressive agents, 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.

Mode of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity

Rheumatoid arthritis

The efficacy of Arava 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.

Psoriatic arthritis

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

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

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 Arava.

Absorption

Excretion data from the ^{14}C study indicated that at least about 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. In multiple dose studies in patients with rheumatoid arthritis, the pharmacokinetic parameters of A771726 were linear over the dose range of 5 to 25 mg. In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

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

Metabolism

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 cholestyramine 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.

Pharmacokinetics in renal failure

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.

Pharmacokinetics in liver failure

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.

Influence of age

Pharmacokinetics in subjects under 18 years have not been studied. 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, leukopenia, 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: Maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, lactose monohydrate.

Film-Coating: Talc, hypromellose, titanium dioxide, macrogol 8000 and yellow ferric oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister: Store in the original package.

Bottle: Keep the container tightly closed.

6.5 Nature and contents of container

Blister: Aluminium / Aluminium blister. Pack sizes: 30 and 100 tablets.

Bottle: HDPE-wide-necked bottle, 100 ml with screw cap with integrated desiccant container. Pack sizes: 30,50 and 100 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/118/005-008
EU/1/99/118/010

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

02.09.1999

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Arava 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of the active ingredient leflunomide.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leflunomide is indicated for the treatment of adult patients with :

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

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

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

4.2 Posology and method of administration

ALT (SGPT) and a complete blood cell count, includinga differential white blood cell count anda 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 also section 4.4).

Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily and is 20 mg once daily for psoriatic arthritis (see section 5.1).

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

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

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

The product should be prescribed by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

Administration

Arava 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

Arava must not be used in patients with hypersensitivity to leflunomide (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients in the tablets.

Leflunomide is contraindicated in:

- patients with impairment of liver function,
- patients with severe immunodeficiency states, e.g. AIDS,
- patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis,
- patients with serious infections,
- 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 also section 4.6). Pregnancy must be excluded before start of treatment with leflunomide.

Women must not breast-feed while they are receiving leflunomide. See also section 4.6.

Male patients should be aware of the possible male-mediated foetal toxicity (see also section 4.4). Reliable contraception during treatment with leflunomide should also be guaranteed.

Arava is not recommended for use in patients under 18 years as its safety and efficacy have not been studied in this age group.

4.4 Special warnings and special precautions for use

Arava should be administered to patients only under careful medical supervision.

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 when switching to another DMARD (e.g. methotrexate) after treatment with leflunomide a washout procedure should be performed (see below).

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 medication 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. Arava 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 anemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of 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, Arava and any concomitant myelosuppressive medication 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 (with the exception of methotrexate, see section 4.5) has not been studied up to now. 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 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 drugs (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, Arava and any other possibly associated medication 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).

Infections

It is known that medications with immunosuppressive properties may - like leflunomide - 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.

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

Respiratory reactions

Interstitial Lung disease has been reported during treatment with leflunomide (see section 4.8). 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.

Blood pressure

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

Procreation (recommendations for men)

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 cholestyramine 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

Cholestyramine 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.

4.5 Interaction with other medicinal products and other forms of interaction

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 cholestyramine 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 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 Arava.

4.6 Pregnancy and lactation

Pregnancy

The active metabolite of leflunomide, A771726, is teratogenic in rats and rabbits and it may cause foetal harm in humans.

Leflunomide must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and for a certain period of time thereafter (waiting period or abbreviated washout period; see below). Pregnancy must be excluded before start of treatment with leflunomide.

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.

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:

- cholestyramine 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 cholestyramine 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 cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Lactation

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

Classification of expected frequencies:

common = 1 - 10 % of patients; uncommon = 0.1 - 1 % of patients; rare = 0.01 - 0.1 % of patients; very rare = 0.01 % of patients or less.

Cardiac disorders

Common: mild increase in blood pressure

Rare: severe increase in blood pressure

Gastrointestinal disorders

Common: diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain,

Hepato-biliary disorders

Common: elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)

Rare: hepatitis, jaundice/cholestasis and very rarely, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal

Very rare: pancreatitis

Infections and infestations

Very 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).

Metabolism and nutrition disorders

Common: weight loss (usually insignificant)

Uncommon: hypokalaemia

Nervous system disorders

Common: headache, dizziness, asthenia, paraesthesia

Uncommon: taste disturbances, anxiety

Very rare: peripheral neuropathy

Musculoskeletal and connective tissue disorders

Common: tenosynovitis

Uncommon: tendon rupture

Skin and subcutaneous tissue disorders

Common: increased hair loss, eczema, dry skin

Uncommon: urticaria

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Immune system disorders

Common: mild allergic reactions, rash (including maculopapular rash), pruritus

Very rare: severe anaphylactic/anaphylactoid reactions

Respiratory, thoracic and mediastinal disorders

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

Blood and lymphatic system disorders

Common: leukopenia (leukocytes >2 G/l)

Uncommon: anaemia, mild thrombocytopenia (platelets <100 G/l)

Rare: eosinophilia, leukopenia (leukocytes <2 G/l), pancytopenia (probably by antiproliferative mechanism)

Very rare: agranulocytosis**,** vasculitis

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

The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some immunosuppressive agents.

Mild hyperlipidaemia may occur. Uric acid levels usually decrease.
Laboratory findings for which a clinical relevance could not be established include small increases in LDH and CK. Mild hypophosphataemia is uncommon.

Marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility cannot be excluded.

The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. If a severe undesirable effect of leflunomide occurs, or if for any other reason A771726 needs to be cleared rapidly from the body, the washout procedure described in section 4.4 has to be followed. The procedure may be repeated as clinically necessary. For suspected severe immunological/allergic reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis, a complete washout is essential.

4.9 Overdose

Symptoms

There have been reports of chronic overdose in patients taking Arava 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, cholestyramine or charcoal is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 g three times a day for 24 hours to three healthy volunteers decreased plasma levels of A771726 by approximately 40% in 24 hours and by 49% to 65% in 48 hours.

Administration of activated charcoal (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 immunosuppressive agents, 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.

Mode of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity

Rheumatoid arthritis

The efficacy of Arava 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.

Psoriatic arthritis

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

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

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 Arava.

Absorption

Excretion data from the ^{14}C study indicated that at least about 82 to 95% of the dose is absorbed. The time to peak plasma concentrations of A771726 is very variable; peak plasma levels can occur between 1 hour and 24 hours after single administration. Leflunomide can be administered with food, since the extent of absorption is comparable in the fed and fasting state. Due to the very long half-life of A771726 (approximately 2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of A771726. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. In multiple dose studies in patients with rheumatoid arthritis, the pharmacokinetic parameters of A771726 were linear over the dose range of 5 to 25 mg. In these studies, the clinical effect was closely related to the plasma concentration of A771726 and to the daily dose of leflunomide. At a dose level of 20 mg/day, average plasma concentration of A771726 at steady state is approximately 35 µg/ml. At steady state plasma levels accumulate about 33- to 35-fold compared with single dose.

Distribution

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

Metabolism

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 cholestyramine 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.

Pharmacokinetics in renal failure

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.

Pharmacokinetics in liver failure

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.

Influence of age

Pharmacokinetics in subjects under 18 years have not been studied. 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, leukopenia, 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: Maize starch, povidone, crospovidone, talc, silica colloidal anhydrous, magnesium stearate, lactose monohydrate.

Film-Coating: Talc, hypromellose, titanium dioxide, macrogol 8000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium / Aluminium blister. Pack size: 3 tablets.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/118/009

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

02.09.1999

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name of the manufacturer responsible for batch release

AVENTIS PHARMA SPECIALITES
56, Route de Choisy au Bac
F-60205 Compiegne Cedex, France

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

Outer packaging (for blister pack)

Arava 10 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 10 mg leflunomide

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main, Germany

EU/1/99/118/001

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Blister foil

Aventis

Arava 10 mg tablets

Leflunomide

Lot

EXP

Outer packaging (for blister foil)

Arava 10 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 10 mg leflunomide

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main, Germany

EU/1/99/118/002

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Blister foil

Aventis

Arava 10 mg tablets

Leflunomide

Lot

EXP

Outer packaging (for bottle)

Arava 10 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 10 mg leflunomide

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main, Germany

EU/1/99/118/003

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Bottle Label

Arava 10 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/003

Keep out of the reach and sight of children

Lot

EXP

Outer packaging (for bottle)

Arava 10 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 10 mg leflunomide

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main, Germany

EU/1/99/118/004

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Bottle Label

Arava 10 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/004

Keep out of the reach and sight of children

Lot

EXP

Outer packaging (for blister pack)

Arava 20 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main, Germany

EU/1/99/118/005

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Blister foil

Aventis

Arava 20 mg tablets

Leflunomide

Lot

EXP

Outer packaging (for blister pack)

Arava 20 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/006

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Blister foil

Aventis

Arava 20 mg tablets

Leflunomide

Lot

EXP

Outer packaging (for bottle)

Arava 20 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/007

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Bottle Label

Arava 20 mg Film-coated tablets

Leflunomide

30 film-coated tablets

Oral use

Keep the container tightly closed

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/007

Keep out of the reach and sight of children

Lot

EXP

Outer packaging (for bottle)

Arava 20 mg Film-coated tablets

Leflunomide

50 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/010

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Bottle Label

Arava 20 mg Film-coated tablets

Leflunomide

50 film-coated tablets

Oral use

Keep the container tightly closed

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/xxx

Keep out of the reach and sight of children

Lot

EXP

Outer packaging (for bottle)

Arava 20 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/008

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Bottle Label

Arava 20 mg Film-coated tablets

Leflunomide

100 film-coated tablets

Oral use

Keep the container tightly closed

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/008

Keep out of the reach and sight of children

Lot

EXP

Outer packaging (for blister pack)

Arava 100 mg Film-coated tablets

Leflunomide

3 film-coated tablets

Oral use

Keep the container tightly closed

Each film-coated tablet contains 20 mg leflunomide

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

EU/1/99/118/009

Keep out of the reach and sight of children

Medicinal product subject to medical prescription

Lot

EXP

Blister foil

Aventis

Arava 100 mg tablets

Leflunomide

Lot

EXP

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Arava 10 mg film-coated tablets
Leflunomide

Each tablet contains 10 mg of the active substance leflunomide.

The other ingredients are: maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, and lactose monohydrate in the tablet core as well as talc, hypromellose, titanium dioxide, and macrogol 8000 in the film-coating.

Marketing authorisation holder:
Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Manufacturer:
AVENTIS PHARMA SPECIALITES
56, Route de Choisy au Bac
F-60205 Compiegne Cedex, France

1. WHAT ARAVA IS AND WHAT IT IS USED FOR

Appearance of the tablets:
Arava 10 mg film-coated tablets are white to almost white and round with a diameter of about 7 mm. Imprint on one side: ZBN.

Pack sizes:
Film-coated tablets for oral use packed in blisters or bottles.
Packs of 30 and 100 tablets are available.

Arava belongs to a group of substances (isoxazole derivatives) which is a class of antirheumatic medicines.

Arava is used for the treatment of adult patients with active rheumatoid arthritis and with active psoriatic arthritis.

2. BEFORE YOU TAKE ARAVA

Do not take Arava:
- if you have ever had an allergic reaction to leflunomide (especially a serious skin reaction) or to any of the other ingredients (which are listed above under "Other ingredients"),
- if you have impairment of liver function or severe hypoproteinaemia (excessive reduction in blood protein concentration, e.g. due to a renal disease). Otherwise, you may experience more side effects,
- if you suffer from a disease which decreases the strength of your immune defences as it is found with certain infections, (e.g. AIDS), otherwise the weakening of your immune defences may worsen,
- if your bone marrow does not work well or if the number of red or white cells in your blood or the number of blood platelets is markedly decreased,
- if you are suffering from a serious infection,
- if you have moderate to severe impairment of kidney function. This is because there is not enough experience in such patients,
- if you are breast-feeding.

Women of childbearing potential must not take Arava without using reliable contraceptive measures. Women must make sure that they are not pregnant before starting treatment with Arava, and must avoid becoming pregnant while taking Arava and for 2 years afterwards. However, this period may be shortened under certain conditions (for more details on pregnancy, see below under "Pregnancy").

Male patients should be aware of a possible risk of malformations in new-born infants and should not take Arava without using reliable contraceptive measures (for more details, see below under "Take special care with Arava").

If you are younger than 18 years of age, it is not recommended that you take Arava. This is because there is not enough experience of its use in children and adolescents.

Take special care with Arava
Before you start to take Arava, and also whilst taking Arava, your doctor will carry out blood tests to monitor your blood cells and your liver at regular intervals. Similarly, your blood pressure will need to be checked regularly as Arava might cause an increase in blood pressure.

In certain circumstances (serious side effects, changing antirheumatic treatment or in case of a desired pregnancy) your doctor will decide that you should take certain medicines which speed up excretion of Arava from your body.

Tell your doctor without any delay if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin). Such symptoms may indicate the development of liver disorders which may need special action by your doctor (see also under point 4).

Tell your doctor without any delay if you have any symptoms suggestive of an infection (e.g. fever, sore throat, cough). This is because some infections might become more severe and, therefore, need early and vigorous treatment if patients are taking medicines that, like Arava, reduce the immune response.

Tell your doctor without any delay if you experience symptoms such as persistent cough, breathing difficulties or shortness of breath. Such symptoms may indicate the development of a potentially serious pulmonary disorder, which needs further action by your doctor. (See also section 4)

Tell your doctor if you have ever suffered from tuberculosis. If you have ever had tuberculosis, your doctor will carefully monitor you, in order to be able to treat you without delay in case it becomes active again.

Tell your doctor without any delay if you have symptoms such as paleness, tiredness, increased proneness to infections or bruising. Such symptoms may point to the existence of blood cell disorders which may need discontinuation of Arava and other medications, and further action by your doctor (see also under point 4).
Tell your doctor without any delay if you develop skin rash or mucous membrane lesions (e.g. lesions in the mouth). This is because, in very rare cases, such reactions may develop into severe, sometimes life-threatening bullous skin and mucous membrane reactions. They may, therefore, require discontinuation of Arava and immediate action by your doctor (see also under point 4).

On the basis of the available information the risk of malformations in new-born infants of men taking Arava cannot be excluded. To minimise any possible risk, men wishing to father a child should contact their doctor. He/she may advise you to stop Arava and take certain medicines to speed up excretion of Arava from your body. It should be confirmed by a laboratory test that Arava has been sufficiently eliminated and you should then wait for at least another 3 months.

Taking Arava with food and drink
It is not recommended to drink alcohol during treatment with Arava. Drinking alcohol while taking Arava may result in harm to your liver more than you would usually expect.

Pregnancy
Make sure that you are not pregnant before you start treatment with Arava because Arava can harm your baby. You are strictly advised against becoming pregnant while taking Arava (see above under "Do not take Arava"). Women must not take Arava without using reliable contraceptive measures when they are of childbearing potential.

If you plan to become pregnant after stopping Arava, it is important to inform your doctor beforehand; after stopping Arava you need to wait for 2 years, but this delay may be shortened to a few weeks by taking certain medicines which speed up excretion of Arava from your body. In either case it should be confirmed by a laboratory test that Arava has been sufficiently eliminated from your body and you should then wait for at least another month before you become pregnant.
For further information on the laboratory testing please contact the Marketing Authorisation Holder or its local representative.

If you suspect that you are pregnant while taking Arava or in the two years after cessation of treatment (e.g. when your period is delayed), you must notify your doctor immediately for pregnancy testing; if the test confirms that you are pregnant, discuss with your doctor the risk of the treatment to your baby. Your doctor may propose at the first delay of menses to initiate the above-mentioned treatment which speeds up excretion of Arava from the body rapidly, as this may decrease the risk to your baby.

Breast-feeding
Do not take Arava when you are breast feeding. Ask your doctor or pharmacist for advice.

Driving and using machines
Some side effects like dizziness may impair your ability to concentrate and react. Do not drive, operate dangerous machinery or undertake similar activities if you feel that your ability to concentrate and react is impaired.

Taking other medicines
Tell your doctor about **all** medicines you are taking or have taken recently including any that you bought without a prescription. This is because the effects of Arava or the other medicines may be changed or you might get side effects. Furthermore, do not take any new medicine without consulting your doctor.

Arava and other medicines for the treatment of rheumatoid arthritis
If you are already taking a nonsteroidal anti-inflammatory drug (NSAID) and/or corticosteroids, you may continue to take them after starting Arava.

Since leflunomide persists in the body over a long period of time, caution is advised in changeover to another slow acting antirheumatic treatment.

Combination of leflunomide with other medicinal products usually given for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate). is not advisable.

Other medicines which may interact with Arava
Cholestyramine (used in the treatment of increased lipid values) and activated charcoal (used in the treatment of diarrhoea) reduce the uptake of Arava and may therefore reduce its therapeutic effect.

When taking Arava together with medicines which have the potential for causing blood or liver side effects, e.g. methotrexate, the possibility of getting such side effects may be increased (your doctor knows these medicines and will advise you accordingly). This is also true for a while after treatment with Arava has been stopped or when such medicines have preceded Arava treatment.

Arava may influence the inactivation of some other medicines by the liver. This is true for phenytoin, warfarin, tolbutamide and other drugs metabolised by a certain enzyme system in the liver (CYP2C9). For such medicines your doctor may want to prescribe a lower dose than usual to prevent side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs; medicines commonly used in rheumatoid arthritis) are not affected.

Vaccinations
If you have to be vaccinated (e.g. for travel outside Europe), ask your doctor for special advice. A vaccination with live attenuated vaccines should not be performed while taking Arava, and for a certain duration after stopping treatment.

3. HOW TO TAKE ARAVA

Your doctor will tell you how many Arava tablets to take, at what time and for how long.

The usual starting dosage of Arava is one 100 mg tablet once daily for the first three days. Thereafter, i.e. from the 4th day onwards, most patients need a dose of :

- 10 to 20 mg Arava per day for the treatment of rheumatoid arthritis,
- 20mg Arava per day for the treatment of active psoriatic arthritis.

Arava may be taken during meals or at any time between meals. Swallow the tablet whole and with sufficient fluid.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.

You will normally take Arava over long periods of time.

If you take more Arava than you should:
If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

In general, an overdose may lead to increased symptoms as described under side effects. In the event of overdose, special drug treatment may be administered by your doctor in order to speed up the elimination of Arava from your body.

If you forget to take Arava:
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not double-up on the next dose to make up for the one missed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Arava may have side effects.
The side effects in this section are given with an estimation of the frequency with which they may occur. For this purpose, the following frequency categories and denominations have been used:

Common: side effects which may occur in 1 to 10 out of 100 patients.
Uncommon: side effects which may occur in less than 1 out of 100 patients.
Rare: side effects which may occur in less than 1 out of 1000 patients.
Very rare: side effects which may occur in less than 1 out of 10,000 patients.
Isolated cases: even more rare.

Common side effects of Arava are: Increased blood pressure (usually mild, while severe increase is rare), diarrhoea, nausea, vomiting, loss of appetite, oral mucosal disorders (e.g., inflammation of the mouth, mouth ulceration), abdominal pain, weight loss (usually insignificant), headache, dizziness, weakness, abnormal skin sensations like tingling (paraesthesia), inflammation of a tendon sheath, increased hair loss, eczema, dry skin.

Also common are mild allergic reactions, rash and itching, whereas occurrence of hives is uncommon. Severe and potentially serious allergic reactions are very rare. Symptoms of severe allergic reactions to any medications include weakness, drop in blood pressure and difficult breathing. If such symptoms do occur, inform your doctor at once, and on no account continue taking the drug without your doctor‘s express guidance.
Occurrence of rash or mucous membrane lesions (e.g. in the mouth) may possibly indicate the development of severe, sometimes life-threatening bullous skin and mucous membrane reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), which are very rare. Therefore, tell your doctor without any delay if you develop skin rash or mucous membrane lesions. They may require discontinuation of Arava and immediate action by your doctor (see also under point 2).

A decrease in the number of white blood cells (leukopenia) is common, a pronounced decrease is, however, rare, as is an increase in the number of so-called eosinophilic blood cells. A decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia) are uncommon. A pronounced reduction in the number of all blood cells (pancytopenia) is rare. Symptoms such as paleness, tiredness, increased proneness to infections or bruising may point to the existence of such blood cell disorders. If such symptoms do occur, inform your doctor at once.

Other uncommon symptoms are: Taste disturbances, anxiety, tendon rupture.

Blood tests may show an increase in some liver test results, which in very rare cases may develop into serious conditions such as hepatitis and liver failure which may be fatal. Therefore, if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin), inform your doctor at once.

An increase in your blood fat levels (cholesterol and triglycerides), or a decrease in the uric acid, potassium or phosphate levels may occur. Small increases in some other laboratory parameters may also be observed.

Like other antirheumatic medicines that to some extent reduce the immune defence, Arava may increase the susceptibility to infections (see under point 2, subsection "Take special care with Arava") and may lead in very rare cases to severe infections including sepsis, which may be life-threatening. If you recognise symptoms of an infection, inform your doctor at once.

Inflammation of the lung (interstitial lung disease) occurs rarely. If you experience cough or breathing problems, inform your doctor at once. (See also section 2, Take special care with Arava)

A slight influence on fertility (a decrease in sperm numbers and motility) cannot be excluded. However, this effect is reversible once treatment with Arava is stopped.
Other very rare side effects are: inflammation of the pancreas (pancreatitis), troubles in the nerves of the arms or legs (peripheral neuropathy), inflammation of the small vessels (vasculitis).

Please consult your doctor or pharmacist if you notice any of the side effects listed in this leaflet, or any other undesired effects or unexpected changes.
If sudden or severe reactions do occur, inform your doctor at once, and on no account continue taking the drug without your doctor‘s express guidance.

5. STORING ARAVA

Keep out of the reach and sight of children.

Blister: Store in the original package in order to protect from moisture.

Bottle: Keep the container tightly closed in order to protect from moisture.

Do not use the tablets after the expiry date shown on the packaging.

Further information
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Aventis Pharma Ltd
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This leaflet was last approved on {date}

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Arava 20 mg film-coated tablets
Leflunomide

Each tablet contains 20 mg of the active substance leflunomide.

The other ingredients are: maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, and lactose monohydrate in the tablet core as well as talc, hypromellose, titanium dioxide, macrogol 8000 and yellow ferric oxide in the film-coating.

Marketing authorisation holder:
Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Manufacturer:
AVENTIS PHARMA SPECIALITES
56, Route de Choisy au Bac
F-60205 Compiegne Cedex, France

1. WHAT ARAVA IS AND WHAT IT IS USED FOR

Appearance of the tablets:
Arava 20 mg film-coated tablets are yellowish to ochre and triangular.
Imprint on one side: ZBO.

Pack sizes:
Film-coated tablets for oral use packed in blisters or bottles.
Packs of 30, 50 and 100 tablets are available.

Arava belongs to a group of substances (isoxazole derivatives) which is a class of antirheumatic medicines.

Arava is used for the treatment of adult patients with active rheumatoid arthritis and with active psoriatic arthritis.

2. BEFORE YOU TAKE ARAVA

Do not take Arava:
- if you have ever had an allergic reaction to leflunomide (especially a serious skin reaction) or to any of the other ingredients (which are listed above under "Other ingredients"),
- if you have impairment of liver function or severe hypoproteinaemia (excessive reduction in blood protein concentration, e.g. due to a renal disease). Otherwise, you may experience more side effects,
- if you suffer from a disease which decreases the strength of your immune defences as it is found with certain infections, (e.g. AIDS), otherwise the weakening of your immune defences may worsen,
- if your bone marrow does not work well or if the number of red or white cells in your blood or the number of blood platelets is markedly decreased,
- if you are suffering from a serious infection,
- if you have moderate to severe impairment of kidney function. This is because there is not enough experience in such patients,
- if you are breast-feeding.

Women of childbearing potential must not take Arava without using reliable contraceptive measures. Women must make sure that they are not pregnant before starting treatment with Arava, and must avoid becoming pregnant while taking Arava and for 2 years afterwards. However, this period may be shortened under certain conditions (for more details on pregnancy, see below under "Pregnancy").

Male patients should be aware of a possible risk of malformations in new-born infants and should not take Arava without using reliable contraceptive measures (for more details, see below under "Take special care with Arava").

If you are younger than 18 years of age, it is not recommended that you take Arava. This is because there is not enough experience of its use in children and adolescents.

Take special care with Arava
Before you start to take Arava, and also whilst taking Arava, your doctor will carry out blood tests to monitor your blood cells and your liver at regular intervals. Similarly, your blood pressure will need to be checked regularly as Arava might cause an increase in blood pressure.

In certain circumstances (serious side effects, changing antirheumatic treatment or in case of a desired pregnancy) your doctor will decide that you should take certain medicines which speed up excretion of Arava from your body.

Tell your doctor without any delay if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin). Such symptoms may indicate the development of liver disorders which may need special action by your doctor (see also under point 4).

Tell your doctor without any delay if you have any symptoms suggestive of an infection (e.g. fever, sore throat, cough). This is because some infections might become more severe and, therefore, need early and vigorous treatment if patients are taking medicines that, like Arava, reduce the immune response.

Tell your doctor without any delay if you experience symptoms such as persistent cough, breathing difficulties or shortness of breath. Such symptoms may indicate the development of a potentially serious pulmonary disorder, which needs further action by your doctor. (See also section 4)

Tell your doctor if you have ever suffered from tuberculosis. If you have ever had tuberculosis, your doctor will carefully monitor you, in order to be able to treat you without delay in case it becomes active again.

Tell your doctor without any delay if you have symptoms such as paleness, tiredness, increased proneness to infections or bruising. Such symptoms may point to the existence of blood cell disorders which may need discontinuation of Arava and other medications, and further action by your doctor (see also under point 4).
Tell your doctor without any delay if you develop skin rash or mucous membrane lesions (e.g. lesions in the mouth). This is because, in very rare cases, such reactions may develop into severe, sometimes life-threatening bullous skin and mucous membrane reactions. They may, therefore, require discontinuation of Arava and immediate action by your doctor (see also under point 4).

On the basis of the available information the risk of malformations in new-born infants of men taking Arava cannot be excluded. To minimise any possible risk, men wishing to father a child should contact their doctor. He/she may advise you to stop Arava and take certain medicines to speed up excretion of Arava from your body. It should be confirmed by a laboratory test that Arava has been sufficiently eliminated and you should then wait for at least another 3 months.

Taking Arava with food and drink
It is not recommended to drink alcohol during treatment with Arava. Drinking alcohol while taking Arava may result in harm to your liver more than you would usually expect.

Pregnancy
Make sure that you are not pregnant before you start treatment with Arava because Arava can harm your baby. You are strictly advised against becoming pregnant while taking Arava (see above under "Do not take Arava"). Women must not take Arava without using reliable contraceptive measures when they are of childbearing potential.

If you plan to become pregnant after stopping Arava, it is important to inform your doctor beforehand; after stopping Arava you need to wait for 2 years, but this delay may be shortened to a few weeks by taking certain medicines which speed up excretion of Arava from your body. In either case it should be confirmed by a laboratory test that Arava has been sufficiently eliminated from your body and you should then wait for at least another month before you become pregnant.
For further information on the laboratory testing please contact the Marketing Authorisation Holder or its local representative.

If you suspect that you are pregnant while taking Arava or in the two years after cessation of treatment (e.g. when your period is delayed), you must notify your doctor immediately for pregnancy testing; if the test confirms that you are pregnant, discuss with your doctor the risk of the treatment to your baby. Your doctor may propose at the first delay of menses to initiate the above-mentioned treatment which speeds up excretion of Arava from the body rapidly, as this may decrease the risk to your baby.

Breast-feeding
Do not take Arava when you are breast feeding. Ask your doctor or pharmacist for advice.

Driving and using machines
Some side effects like dizziness may impair your ability to concentrate and react. Do not drive, operate dangerous machinery or undertake similar activities if you feel that your ability to concentrate and react is impaired.

Taking other medicines
Tell your doctor about **all** medicines you are taking or have taken recently including any that you bought without a prescription. This is because the effects of Arava or the other medicines may be changed or you might get side effects. Furthermore, do not take any new medicine without consulting your doctor.

Arava and other medicines for the treatment of rheumatoid arthritis
If you are already taking a nonsteroidal anti-inflammatory drug (NSAID) and/or corticosteroids, you may continue to take them after starting Arava.

Since leflunomide persists in the body over a long period of time, caution is advised in changeover to another slow acting antirheumatic treatment.

Combination of leflunomide with other medicinal products usually given for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate). is not advisable.

Other medicines which may interact with Arava
Cholestyramine (used in the treatment of increased lipid values) and activated charcoal (used in the treatment of diarrhoea) reduce the uptake of Arava and may therefore reduce its therapeutic effect.

When taking Arava together with medicines which have the potential for causing blood or liver side effect, e.g. methotrexate, the possibility of getting such side effects may be increased (your doctor knows these medicines and will advise you accordingly). This is also true for a while after treatment with Arava has been stopped or when such medicines have preceded Arava treatment.

Arava may influence the inactivation of some other medicines by the liver. This is true for phenytoin, warfarin, tolbutamide and other drugs metabolised by a certain enzyme system in the liver (CYP2C9). For such medicines your doctor may want to prescribe a lower dose than usual to prevent side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs; medicines commonly used in rheumatoid arthritis) are not affected.

Vaccinations
If you have to be vaccinated (e.g. for travel outside Europe), ask your doctor for special advice. A vaccination with live attenuated vaccines should not be performed while taking Arava, and for a certain duration after stopping treatment.

3. HOW TO TAKE ARAVA

Your doctor will tell you how many Arava tablets to take, at what time and for how long.

The usual starting dosage of Arava is one 100 mg tablet once daily for the first three days. Thereafter, i.e. from the 4th day onwards, most patients need a dose of :

- 10 to 20 mg Arava per day for the treatment of rheumatoid arthritis,
- 20 mg Arava per day for the treatment of active psoriatic arthritis.

Arava may be taken during meals or at any time between meals. Swallow the tablet whole and with sufficient fluid.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.

You will normally take Arava over long periods of time.

If you take more Arava than you should:
If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

In general, an overdose may lead to increased symptoms as described under side effects. In the event of overdose, special drug treatment may be administered by your doctor in order to speed up the elimination of Arava from your body.

If you forget to take Arava:
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not double-up on the next dose to make up for the one missed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Arava may have side effects.
The side effects in this section are given with an estimation of the frequency with which they may occur. For this purpose, the following frequency categories and denominations have been used:

Common: side effects which may occur in 1 to 10 out of 100 patients.
Uncommon: side effects which may occur in less than 1 out of 100 patients.
Rare: side effects which may occur in less than 1 out of 1000 patients.
Very rare: side effects which may occur in less than 1 out of 10,000 patients.
Isolated cases: even more rare.

Common side effects of Arava are: Increased blood pressure (usually mild, while severe increase is rare), diarrhoea, nausea, vomiting, loss of appetite, oral mucosal disorders (e.g., inflammation of the mouth, mouth ulceration), abdominal pain, weight loss (usually insignificant), headache, dizziness, weakness, abnormal skin sensations like tingling (paraesthesia), inflammation of a tendon sheath, increased hair loss, eczema, dry skin.

Also common are mild allergic reactions, rash and itching, whereas occurrence of hives is uncommon. Severe and potentially serious allergic reactions are very rare. Symptoms of severe allergic reactions to any medications include weakness, drop in blood pressure and difficult breathing. If such symptoms do occur, inform your doctor at once, and on no account continue taking the drug without your doctor‘s express guidance.
Occurrence of rash or mucous membrane lesions (e.g. in the mouth) may possibly indicate the development of severe, sometimes life-threatening bullous skin and mucous membrane reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), which are very rare. Therefore, tell your doctor without any delay if you develop skin rash or mucous membrane lesions. They may require discontinuation of Arava and immediate action by your doctor (see also under point 2).

A decrease in the number of white blood cells (leukopenia) is common, a pronounced decrease is, however, rare, as is an increase in the number of so-called eosinophilic blood cells. A decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia) are uncommon. A pronounced reduction in the number of all blood cells (pancytopenia) is rare. Symptoms such as paleness, tiredness, increased proneness to infections or bruising may point to the existence of such blood cell disorders. If such symptoms do occur, inform your doctor at once.

Other uncommon symptoms are: Taste disturbances, anxiety, tendon rupture.

Blood tests may show an increase in some liver test results, which in very rare cases may develop into serious conditions such as hepatitis and liver failure which may be fatal. Therefore, if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin), inform your doctor at once.

An increase in your blood fat levels (cholesterol and triglycerides), or a decrease in the uric acid, potassium or phosphate levels may occur. Small increases in some other laboratory parameters may also be observed.

Like other antirheumatic medicines that to some extent reduce the immune defence, Arava may increase the susceptibility to infections (see under point 2, subsection "Take special care with Arava") and may lead in very rare cases to severe infections including sepsis, which may be life-threatening. If you recognise symptoms of an infection, inform your doctor at once.

Inflammation of the lung (interstitial lung disease) occurs rarely. If you experience cough or breathing problems, inform your doctor at once. (See also section 2, Take special care with Arava)

A slight influence on fertility (a decrease in sperm numbers and motility) cannot be excluded. However, this effect is reversible once treatment with Arava is stopped.
Other very rare side effects are: inflammation of the pancreas (pancreatitis), troubles in the nerves of the arms or legs (peripheral neuropathy), inflammation of the small vessels (vasculitis).

Please consult your doctor or pharmacist if you notice any of the side effects listed in this leaflet, or any other undesired effects or unexpected changes.
If sudden or severe reactions do occur, inform your doctor at once, and on no account continue taking the drug without your doctor‘s express guidance.

5. STORING ARAVA

Keep out of the reach and sight of children.

Blister: Store in the original package in order to protect from moisture.

Bottle: Keep the container tightly closed in order to protect from moisture.

Do not use the tablets after the expiry date shown on the packaging.

Further information
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Arava 100 mg film-coated tablets
Leflunomide

Each tablet contains 100 mg of the active substance leflunomide.

The other ingredients are: maize starch, povidone, crospovidone, talc, silica colloidal anhydrous, magnesium stearate, and lactose monohydrate in the tablet core as well as talc, hypromellose, titanium dioxide, and macrogol 8000 in the film-coating.

Marketing authorisation holder:
Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Manufacturer:
AVENTIS PHARMA SPECIALITES
56, Route de Choisy au Bac
F-60205 Compiegne Cedex, France

1. WHAT ARAVA IS AND WHAT IT IS USED FOR

Appearance of the tablets:
Arava 100 mg film-coated tablets are white to almost white and round with a diameter of about 1 cm. Imprint on one side: ZBP.

Pack sizes:
Film-coated tablets for oral use packed in blisters.
A pack of 3 tablets is available.

Arava belongs to a group of substances (isoxazole derivatives) which is a class of antirheumatic medicines.

Arava is used for the treatment of adult patients with active rheumatoid arthritis and with active psoriatic arthritis.

2. BEFORE YOU TAKE ARAVA

Do not take Arava:
- if you have ever had an allergic reaction to leflunomide (especially a serious skin reaction) or to any of the other ingredients (which are listed above under "Other ingredients"),
- if you have impairment of liver function or severe hypoproteinaemia (excessive reduction in blood protein concentration, e.g. due to a renal disease). Otherwise, you may experience more side effects,
- if you suffer from a disease which decreases the strength of your immune defences as it is found with certain infections, (e.g. AIDS), otherwise the weakening of your immune defences may worsen,
- if your bone marrow does not work well or if the number of red or white cells in your blood or the number of blood platelets is markedly decreased,
- if you are suffering from a serious infection,
- if you have moderate to severe impairment of kidney function. This is because there is not enough experience in such patients,
- if you are breast-feeding.

Women of childbearing potential must not take Arava without using reliable contraceptive measures. Women must make sure that they are not pregnant before starting treatment with Arava, and must avoid becoming pregnant while taking Arava and for 2 years afterwards. However, this period may be shortened under certain conditions (for more details on pregnancy, see below under "Pregnancy").

Male patients should be aware of a possible risk of malformations in new-born infants and should not take Arava without using reliable contraceptive measures (for more details, see below under "Take special care with Arava").

If you are younger than 18 years of age, it is not recommended that you take Arava. This is because there is not enough experience of its use in children and adolescents.

Take special care with Arava
Before you start to take Arava, and also whilst taking Arava, your doctor will carry out blood tests to monitor your blood cells and your liver at regular intervals. Similarly, your blood pressure will need to be checked regularly as Arava might cause an increase in blood pressure.

In certain circumstances (serious side effects, changing antirheumatic treatment or in case of a desired pregnancy) your doctor will decide that you should take certain medicines which speed up excretion of Arava from your body.

Tell your doctor without any delay if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin). Such symptoms may indicate the development of liver disorders which may need special action by your doctor (see also under point 4).

Tell your doctor without any delay if you have any symptoms suggestive of an infection (e.g. fever, sore throat, cough). This is because some infections might become more severe and, therefore, need early and vigorous treatment if patients are taking medicines that, like Arava, reduce the immune response.

Tell your doctor without any delay if you experience symptoms such as persistent cough, breathing difficulties or shortness of breath. Such symptoms may indicate the development of a potentially serious pulmonary disorder, which needs further action by your doctor. (See also section 4)

Tell your doctor if you have ever suffered from tuberculosis. If you have ever had tuberculosis, your doctor will carefully monitor you, in order to be able to treat you without delay in case it becomes active again.

Tell your doctor without any delay if you have symptoms such as paleness, tiredness, increased proneness to infections or bruising. Such symptoms may point to the existence of blood cell disorders which may need discontinuation of Arava and other medications, and further action by your doctor (see also under point 4).
Tell your doctor without any delay if you develop skin rash or mucous membrane lesions (e.g. lesions in the mouth). This is because, in very rare cases, such reactions may develop into severe, sometimes life-threatening bullous skin and mucous membrane reactions. They may, therefore, require discontinuation of Arava and immediate action by your doctor (see also under point 4).

On the basis of the available information the risk of malformations in new-born infants of men taking Arava cannot be excluded. To minimise any possible risk, men wishing to father a child should contact their doctor. He/she may advise you to stop Arava and take certain medicines to speed up excretion of Arava from your body. It should be confirmed by a laboratory test that Arava has been sufficiently eliminated and you should then wait for at least another 3 months.

Taking Arava with food and drink
It is not recommended to drink alcohol during treatment with Arava. Drinking alcohol while taking Arava may result in harm to your liver more than you would usually expect.

Pregnancy
Make sure that you are not pregnant before you start treatment with Arava because Arava can harm your baby. You are strictly advised against becoming pregnant while taking Arava (see above under "Do not take Arava"). Women must not take Arava without using reliable contraceptive measures when they are of childbearing potential.

If you plan to become pregnant after stopping Arava, it is important to inform your doctor beforehand; after stopping Arava you need to wait for 2 years, but this delay may be shortened to a few weeks by taking certain medicines which speed up excretion of Arava from your body. In either case it should be confirmed by a laboratory test that Arava has been sufficiently eliminated from your body and you should then wait for at least another month before you become pregnant.
For further information on the laboratory testing please contact the Marketing Authorisation Holder or its local representative.

If you suspect that you are pregnant while taking Arava or in the two years after cessation of treatment (e.g. when your period is delayed), you must notify your doctor immediately for pregnancy testing; if the test confirms that you are pregnant, discuss with your doctor the risk of the treatment to your baby. Your doctor may propose at the first delay of menses to initiate the above-mentioned treatment which speeds up excretion of Arava from the body rapidly, as this may decrease the risk to your baby.

Breast-feeding
Do not take Arava when you are breast feeding. Ask your doctor or pharmacist for advice.

Driving and using machines
Some side effects like dizziness may impair your ability to concentrate and react. Do not drive, operate dangerous machinery or undertake similar activities if you feel that your ability to concentrate and react is impaired.

Taking other medicines
Tell your doctor about **all** medicines you are taking or have taken recently including any that you bought without a prescription. This is because the effects of Arava or the other medicines may be changed or you might get side effects. Furthermore, do not take any new medicine without consulting your doctor.

Arava and other medicines for the treatment of rheumatoid arthritis
If you are already taking a nonsteroidal anti-inflammatory drug (NSAID) and/or corticosteroids, you may continue to take them after starting Arava.

Since leflunomide persists in the body over a long period of time, caution is advised in changeover to another slow acting antirheumatic treatment.

Combination of leflunomide with other medicinal products usually given for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive drugs (e.g. methotrexate). is not advisable.

Other medicines which may interact with Arava
Cholestyramine (used in the treatment of increased lipid values) and activated charcoal (used in the treatment of diarrhoea) reduce the uptake of Arava and may therefore reduce its therapeutic effect.

When taking Arava together with medicines which have the potential for causing blood or liver side effects, e.g. methotrexate, the possibility of getting such side effects may be increased (your doctor knows these medicines and will advise you accordingly). This is also true for a while after treatment with Arava has been stopped or when such medicines have preceded Arava treatment.

Arava may influence the inactivation of some other medicines by the liver. This is true for phenytoin, warfarin, tolbutamide and other drugs metabolised by a certain enzyme system in the liver (CYP2C9). For such medicines your doctor may want to prescribe a lower dose than usual to prevent side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs; medicines commonly used in rheumatoid arthritis) are not affected.

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If you have to be vaccinated (e.g. for travel outside Europe), ask your doctor for special advice. A vaccination with live attenuated vaccines should not be performed while taking Arava, and for a certain duration after stopping treatment.

3. HOW TO TAKE ARAVA

Your doctor will tell you how many Arava tablets to take, at what time and for how long.

The usual starting dosage of Arava is one 100 mg tablet once daily for the first three days. Thereafter, i.e. from the 4th day onwards, most patients need a dose of :

- 10 to 20 mg Arava per day for the treatment of rheumatoid arthritis,
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Arava may be taken during meals or at any time between meals. Swallow the tablet whole and with sufficient fluid.

It may take about 4 weeks or longer until you start to feel an improvement in your condition. Some patients may even still feel further improvements after 4 to 6 months of therapy.

You will normally take Arava over long periods of time.

If you take more Arava than you should:
If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or get other medical advice. If possible, take your tablets or the box with you to show the doctor.

In general, an overdose may lead to increased symptoms as described under side effects. In the event of overdose, special drug treatment may be administered by your doctor in order to speed up the elimination of Arava from your body.

If you forget to take Arava:
If you forget to take a dose, take it as soon as you remember, unless it is nearly time for your next dose. Do not double-up on the next dose to make up for the one missed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Arava may have side effects.
The side effects in this section are given with an estimation of the frequency with which they may occur. For this purpose, the following frequency categories and denominations have been used:

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Very rare: side effects which may occur in less than 1 out of 10,000 patients.
Isolated cases: even more rare.

Common side effects of Arava are: Increased blood pressure (usually mild, while severe increase is rare), diarrhoea, nausea, vomiting, loss of appetite, oral mucosal disorders (e.g., inflammation of the mouth, mouth ulceration), abdominal pain, weight loss (usually insignificant), headache, dizziness, weakness, abnormal skin sensations like tingling (paraesthesia), inflammation of a tendon sheath, increased hair loss, eczema, dry skin.

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A decrease in the number of white blood cells (leukopenia) is common, a pronounced decrease is, however, rare, as is an increase in the number of so-called eosinophilic blood cells. A decrease in the number of red blood cells (anaemia) and a decrease in the number of blood platelets (thrombocytopenia) are uncommon. A pronounced reduction in the number of all blood cells (pancytopenia) is rare. Symptoms such as paleness, tiredness, increased proneness to infections or bruising may point to the existence of such blood cell disorders. If such symptoms do occur, inform your doctor at once.

Other uncommon symptoms are: Taste disturbances, anxiety, tendon rupture.

Blood tests may show an increase in some liver test results, which in very rare cases may develop into serious conditions such as hepatitis and liver failure which may be fatal. Therefore, if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin), inform your doctor at once.

An increase in your blood fat levels (cholesterol and triglycerides), or a decrease in the uric acid, potassium or phosphate levels may occur. Small increases in some other laboratory parameters may also be observed.

Like other antirheumatic medicines that to some extent reduce the immune defence, Arava may increase the susceptibility to infections (see under point 2, subsection "Take special care with Arava") and may lead in very rare cases to severe infections including sepsis, which may be life-threatening. If you recognise symptoms of an infection, inform your doctor at once.

Inflammation of the lung (interstitial lung disease) occurs rarely. If you experience cough or breathing problems, inform your doctor at once. (See also section 2, Take special care with Arava)

A slight influence on fertility (a decrease in sperm numbers and motility) cannot be excluded. However, this effect is reversible once treatment with Arava is stopped.
Other very rare side effects are: inflammation of the pancreas (pancreatitis), troubles in the nerves of the arms or legs (peripheral neuropathy), inflammation of the small vessels (vasculitis).

Please consult your doctor or pharmacist if you notice any of the side effects listed in this leaflet, or any other undesired effects or unexpected changes.
If sudden or severe reactions do occur, inform your doctor at once, and on no account continue taking the drug without your doctor‘s express guidance.

5. STORING ARAVA

Keep out of the reach and sight of children.

Store in the original package in order to protect from moisture.

Do not use the tablets after the expiry date shown on the packaging.

Further information
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