SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ARAVA 10 mg tablets

ARAVA 20 mg tablets

ARAVA 100 mg tablets

COMPOSITION:

ARAVA 10 mg: Each tablet contains 10 mg Leflunomide

ARAVA 20 mg: Each tablet contains 20 mg Leflunomide

ARAVA 100 mg: Each tablet contains 100 mg Leflunomide

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Antirheumatoids (anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Mode of action: Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in *de novo* pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.

Pharmacokinetic properties: Following oral administration, leflunomide is metabolised to the

active primary metabolite that is responsible for essentially all of its activity *in vivo*. Plasma levels of leflunomide are occasionally seen at very low levels. Studies of the

pharmacokinetics of leflunomide have primarily examined the plasma concentrations of this active metabolite.

Absorption: Following oral administration, peak levels of the primary metabolite occurred between 6 to 12 hours after dosing. Due to the very long half-life of the primary metabolite (approx. 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. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly 2 months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that the primary

metabolite levels are dose proportional. Relative to an oral solution, leflunomide tablets are 80% bioavailable. Co-administration of leflunomide tablets with a high fat meal did not have a significant impact on the primary metabolite plasma levels.

Distribution: The primary metabolite has a low volume of distribution (Vss = 0,13 λ/kg) and is

extensively bound (> 99,3 %) to albumin in healthy subjects. Protein binding has been shown to be linear at therapeutic concentrations. The free fraction of the primary metabolite is slightly higher in patients with RA and approximately doubled in patients with chronic renal failure; the mechanism and significance of these increases are unknown.

Metabolism: Leflunomide is metabolised to one primary and many minor metabolites. Of these minor metabolites, only 4-trifluoromethylaniline (TFMA) is quantifiable, occurring at low levels in the plasma of some patients. The parent compound is rarely detectable in plasma. At the present time, the specific site of leflunomide metabolism is unknown. *In vivo* and *in vitro* studies suggest a role for both the GI wall and the liver in drug metabolism. No specific enzyme has been identified as the primary route of metabolism for leflunomide; however, hepatic cytosolic and microsomal cellular fractions have been identified as sites of drug metabolism.

Elimination: The primary metabolite is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. In a 28 day study of drug elimination (n=3) using a single dose of radiolabelled compound, approximately 43 % of the total radioactivity was eliminated in the urine and 48 % was eliminated in the faeces. Subsequent analysis of the samples revealed the primary urinary metabolites to be leflunomide glucuronides and an oxanilic acid derivative of the primary metabolite. The primary faecal metabolite was the primary metabolite. Of these two routes of elimination, renal elimination is more significant over the first 96 hours, after which faecal elimination begins to predominate. In a study involving the intravenous administration of the primary metabolite, the clearance was estimated to be 31ml/h. In small studies using activated charcoal or cholestyramine to facilitate drug elimination, the *in vivo* plasma half-life of the primary metabolite was reduced from > 1 week to approximately 1 day. Similar reductions in plasma half-life were observed for a series of volunteers (n=96) enrolled in pharmacokinetic trials who were given cholestyramine. This suggests that biliary recycling is a major contributor to the long elimination half-life of the primary metabolite. Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that the primary metabolite cannot be removed by dialysis.

INDICATIONS:

ARAVA is indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD), and to improve physical function.

CONTRA-INDICATIONS:

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.

ARAVA is contra-indicated 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 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 nephritic 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. Pregnancy must be excluded before start of treatment with leflunomide. In animal studies leflunomide was teratogenic in rats and rabbits (refer to Pregnancy and Lactation).

Women must not breast-feed while they are receiving ARAVA.

Male patients should be aware of the possible male-mediated fetal toxicity. Reliable contraception during treatment with ARAVA should also be guaranteed.

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

WARNINGS:

Recent treatment with hepatotoxic or haematotoxic DMARDs may result in increased side-effects;

therefore, the initiation of ARAVA treatment has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from ARAVA to another DMARD without a washout period may increase the possibility of additive risks of side-effects for a long time after the switching.

The active metabolite of ARAVA 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 ARAVA has been stopped. Therefore, when such toxicities occur or when switching to another DMARD (e.g. methotrexate) after treatment with ARAVA or in case of a desired pregnancy a washout procedure should be performed. For washout procedures in case of desired pregnancy, refer to Pregnancy and Lactation.

Recommendations for monitoring and washout procedures:

Monitoring recommendations:

ARAVA should be administered to patients only under careful medical supervision. ALT (SGPT) must be checked before initiation of treatment and at least at monthly intervals during the first six months of treatment and every 6 – 8 weeks thereafter. For confirmed ALT (SGPT) elevations between 2 and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may allow continued administration of leflunomide under close monitoring. If ALT (SGPT) elevations between 2 and 3-fold the upper limit of normal persist or if confirmed ALT elevations of more than 3-fold

the upper limit of normal are present, leflunomide should be discontinued. Cholestyramine or activated charcoal should be administered to more rapidly lower the levels of the active metabolite.

Blood pressure must be checked before the start of ARAVA treatment and periodically thereafter, as increases in blood pressure may occur.

A complete blood cell count, including differential white blood cell count and platelets, must be performed before start of ARAVA treatment as well as monthly for the first 6 months of treatment and every 6 – 8 weeks thereafter.

Combinations with other treatments:

The use of ARAVA 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) 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.

Switching to other treatments:

As ARAVA has a long persistence in the body, a switching to another DMARD (e.g. methotrexate) without a washout period may increase 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 ARAVA treatment has to carefully be considered regarding these benefit/risk aspects.

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.

Liver reactions:

Since the active metabolite of leflunomide (the primary metabolite) is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of the primary metabolite are expected to be increased in patients with hypoproteinaemia or impairment of liver function. ARAVA is contra-indicated in patients with severe hypoproteinaemia or impairment of liver function (refer to Contra-indications). Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with ARAVA.

Haematological reactions:

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

In case of severe haematological reactions including pancytopenia, ARAVA and any concomitant myelosuppressive medication must be discontinued and an ARAVA washout procedure initiated.

Skin reactions:

In case of ulcerative stomatitis, ARAVA administration should be discontinued. Very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with ARAVA. 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 an ARAVA washout procedure initiated immediately. A complete washout is essential in such cases. In such cases re-exposure to leflunomide is contra-indicated (refer to Contra-indications).

Infections:

It is known that medications with immunosuppressive properties 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 stop ARAVA and administer a washout with cholestyramine as described above. Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

Interactions:

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

Procreation (recommendations for men):

There is no specific data on the risk of male-mediated fetal 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 ARAVA and taking cholestyramine 8 g, three times daily for 11 days or 50 g of activated powdered charcoal, four times daily for 11 days. In either case the primary metabolite plasma concentration is then measured for the first time. Thereafter, the primary metabolite 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 fetal toxicity is very low.

INTERACTIONS:

Increased side-effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol), haematotoxic or immunosuppressive substances. This is also to be considered when leflunomide treatment is followed by such substances without a washout period.

In a small (n=30) study with co-administration of ARAVA (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 in 5 of 30 patients. All elevations resolved, 2 with continuation of both medicines and 3 after discontinuation of ARAVA. 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 ARAVA. Therefore, closer monitoring of liver enzymes is recommended in the initial phase after switching.

No pharmacokinetic interaction between ARAVA (10 mg to 20 mg per day) and methotrexate (10 mg to 25 mg per week) was demonstrated. *In vivo* drug interaction studies have demonstrated a lack of significant drug interaction between ARAVA and triphasic oral contraceptives. In a study in which ARAVA 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 the primary metabolite pharmacokinetics were within predicted ranges.

The extent of ARAVA absorption is not affected when taken with food.

No difference in clinical efficacy was seen between smokers and non-smokers.

The enzymes involved in the metabolism of ARAVA 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 ARAVA to subjects receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer), the primary metabolite peak levels were increased by approximately 40 %, whereas the AUC was not significantly changed. The mechanism of this effect is unclear.

The potential for ARAVA levels to continue to increase with multiple dosing may need to be considered if patients are to be receiving both ARAVA and rifampicin.

Phenytoin, tolbutamide, warfarin and many NSAIDs are metabolised by cytochrome P450 2C9 (CYP2C9). *In vitro* studies indicate that the primary metabolite inhibits CYP2C9 activity. The clinical significance of this finding with regard to phenytoin and tolbutamide is unknown. Caution is advised when these agents are given in combination. In clinical trials no safety problems were observed when NSAIDs metabolised by CYP2C9, and ARAVA were co-administered. There have been case reports of increased prothrombin time, when ARAVA and warfarin were co-administered.

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

Administration of cholestyramine or activated charcoal leads to a rapid and significant decrease in plasma primary metabolite concentration. The mechanism is thought to be by

interruption of enterohepatic recycling and/or gastrointestinal dialysis of the primary metabolite. ARAVA should not be given to patients using cholestyramine.

PREGNANCY AND LACTATION:

Pregnancy: The active metabolite of leflunomide is teratogenic in rats and rabbits and it may cause fetal harm in humans. ARAVA must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with ARAVA and for a certain period of time thereafter. Pregnancy must be excluded before start of treatment with ARAVA.

Suspected pregnancy or women deciding to fall pregnant: Patients 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 fetus from ARAVA.

Washout procedure: For women receiving ARAVA treatment and who wish to become pregnant, one of the following procedures is recommended:

- after stopping treatment with leflunomide, cholestyramine 8 g is administered three times daily for
  a period of 11 days.
- after stopping treatment with leflunomide, 50 g of activated charcoal is administered four times daily for a period of 11 days.

The 11 days need not be consecutive unless there is a need to lower the primary metabolite plasma level rapidly. In either case, the primary metabolite plasma levels < 0,02 mg/l must be verified by two separate tests at least 14 days apart. Human plasma levels of the active metabolite less than 0,02 mg/l (0,02 µg/ml) are expected to have minimal risk based on available data.

Without the drug elimination procedure, it may take up to 2 years to reach the primary metabolite levels of < 0,02 mg/l, due to individual variation in drug clearance. However, also after such a waiting period, verification of the primary metabolite levels of < 0,02 mg/l by two separate tests at an interval of at least 14 days is required. If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedure may be advisable. Reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with cholestyramine or activated 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 ARAVA.

DOSAGE AND DIRECTIONS FOR USE:

ARAVA treatment should be initiated by physicians experienced in the therapy of rheumatoid diseases.

For monitoring recommendations refer to Warnings.

ARAVA therapy is started with a loading dose of 100 mg once daily for 3 days.

The recommended maintenance dose is ARAVA tablets 10 mg to 20 mg once daily.

A 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 diseases.

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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

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

The incidence of side-effects is from clinical studies for up to two years.

Side-effects:

Gastrointestinal system, liver:

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

Rare: Hepatitis, jaundice/ cholestasis.

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

In clinical trials, ARAVA treatment was associated with elevations of liver enzymes (refer to Warnings).

Cardiovascular system:

Common: Increase in blood pressure.

Haemic and lymphatic system:

Common: Leukopenia with leucocyte count > 2 x 10^9/l (> 2 G/l).

Uncommon: Anaemia, thrombocytopenia with platelet count < 100 x 10^9/l (< 100 G/l).

Rare: Leukopenia with leucocyte count < 2 x 10^9/l (< 2 G/l), eosinophilia. Pancytopenia.

Very rare: Agranulocytosis.

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

Nervous system:

Common: Headache, dizziness, paraesthesia.

Uncommon: Taste disturbances, anxiety.

Very rare: Peripheral neuropathy.

Allergic reactions, skin and appendages:

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

Uncommon: Urticaria.

Very rare: Severe anaphylactic/anaphylactoid reactions. Stevens-Johnson syndrome (erythema multiforme of major type), toxic epidermal necrolysis. In case reports received so far, a causal relationship with ARAVA treatment could not be established, but cannot be excluded.

Very rare: Vasculitis, including cutaneous necrotizing vasculitis.

Infections:

Severe infections and sepsis, which may be fatal.

Immunosuppressive medications are known to increase susceptibility to infections, including opportunistic infections and infections with atypical organisms. In clinical studies, the incidence of, for example rhinitis (5 % vs. 2 %) and bronchitis (5 % vs. 2 %), and pneumonia (3 % vs. 0 %) was slightly increased in patients treated with ARAVA compared to placebo, whereas the overall incidence of infections was comparable to placebo.

Respiratory, thoracic and mediastinal disorders:

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

Others:

Common: Weight loss, asthenia.

Uncommon: Hypokalaemia.

Mild hyperlipidaemia may occur.

Uric acid levels usually decrease, due to a uricosuric effect.

Possible further laboratory findings for which a clinical relevance could not be established include: small increases in LDH and creatinine kinase (CK), and a small decrease in phosphate.

The risk of malignancy, particularly lymphoproliferative disorders, is also known to be increased with use of some immunosuppressive drugs.

Special precautions:

General:

Due to the prolonged half-life of the active metabolite of ARAVA , adverse reactions may

occur or persist even after ARAVA administration has been discontinued.

If a severe adverse reaction to ARAVA occurs, or if for any other reason the primary metabolite needs to be cleared rapidly from the body, a washout procedure as described under “Known symptoms of overdosage and particulars of its treatment” and “Warnings”, has to be initiated and continued/repeated as clinically necessary. For suspected severe immunologic/allergic reactions, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance.

Liver: The active metabolite of ARAVA (the primary metabolite) is highly protein bound and cleared via hepatic metabolism and biliary secretion, thus ARAVA should be used with caution in patients with impairment of liver function. ARAVA is contra-indicated in patients with hepatic impairment or pre-existing hepatic disease.

Rare cases of serious liver injury, in isolated cases with fatal outcome, have been reported during treatment with ARAVA. Most of the cases occurred within the first 6 months of treatment. Although a causal relationship to ARAVA has not been established and multiple confounding factors were present in most cases, it is considered essential that monitoring recommendations are closely followed.

Haematopoetic and immune system: In patients with pre-existing anaemia, leukopenia and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk for occurrence of haematological reactions is increased.

Frequent haematological monitoring (complete blood cell count, including differential white blood cell count and platelet count) should be performed in:

- patients with recent or concomitant treatment with immunosuppressive or haematotoxic drugs, and when ARAVA treatment is followed by such substances without a washout period.
- patients with a history of relevant haematological abnormalities.
- patients with relevant haematological abnormalities at baseline due to causes other than rheumatoid arthritis.

Due to the potential for immunosuppression, although there is no clinical experience, ARAVA is not recommended in patients with:

- severe immunodefiency (e.g. AIDS).

- significant impairment of bone marrow function.
- serious infections.

Infections:

Medications like ARAVA that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections and these may be more severe in nature (refer to Side-effects). Infections may, therefore, require early and vigorous treatment. In the event that a serious infection occurs, it may be necessary to interrupt ARAVA treatment and administer a washout procedure as described under Warnings.

Respiratory:

Interstitial lung disease has been reported rarely during treatment with ARAVA. Interstitial lung disease is a potentially fatal disorder, which may occur acutely during therapy. Patients should be warned to report pulmonary symptoms, such as cough and dyspnoea, which should be further investigated to exclude interstitial lung disease. If interstitial lung disease is suspected, ARAVA should be discontinued and patients should be further investigated as appropriate.

It is recommended that patients with tuberculin reactivity be carefully monitored because of the risk of tuberculosis reactivation.

Renal impairment: At present there is insufficient experience available to make specific dosage

recommendations for patients with renal impairment. Caution should be used when administering ARAVA in this population. It should be considered that the active metabolite of ARAVA is highly protein bound.

Use in males: Available information does not suggest that ARAVA would be associated with an increased risk of male-mediated fetal 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 ARAVA and go through the drug elimination procedure described under warnings.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There have been reports of accidental overdose in patients taking ARAVA at daily doses up to five times the recommended daily dose for several days and reports of acute overdose in adults or children. There were no adverse events reported in the majority of case reports of overdose. Adverse events were consistent with the adverse effects profile for ARAVA. The most frequent adverse events observed were diarrhoea, abdominal pain, leukopenia, anaemia and elevated liver function tests.

In the event of relevant overdose or toxicity, cholestyramine or charcoal must be given 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 the primary metabolite by approximately 40 % in 24 hours and by 49 to 65 % in 48 hours. Administration of activated charcoal, orally or via a nasogastric tube at a dose of 50 g every six hours for 24 hours, has been shown to reduce plasma concentrations of the active metabolite by 37 % in 24 hours and by 48 % in 48 hours.

The washout procedures may be repeated if clinically necessary.

IDENTIFICATION:

ARAVA 10 mg: white to almost white, round, film-coated tablets with a diameter of 7 mm.

Embossment: ZBN

ARAVA 20 mg: yellowish to ochre, spherical, triangular, film-coated tablets with a height of 7 mm. Embossment: ZBO

ARAVA 100 mg: white to almost white, round, film-coated tablets with a diameter of 9.5 mm. Embossment: ZBP

PRESENTATION:

ARAVA 10 mg: 30 tablets in plastic bottles

ARAVA 20 mg: 30 tablets in plastic bottles

ARAVA 100 mg: 3 tablets in blisters

STORAGE INSTRUCTIONS:

Store below 25 °C.

Bottles should be kept tightly closed.

Blister packs must be stored in the original package.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ARAVA 10 mg: 33/3.1/0290

ARAVA 20 mg: 33/3.1/0291

ARAVA 100 mg: 33/3.1/0292

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd

2 Bond Street, Midrand, South Africa, 1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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