PART III: CONSUMER INFORMATION

Pr**ARAVA®**
Leflunomide, Mfr. Std.

This leaflet is part III of a three-part "Product Monograph" published when ARAVA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ARAVA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

IMPORTANT INFORMATION AND WARNING: ARAVA may cause severe birth defects

What the medication is used for:

ARAVA is used to treat adult patients who have active rheumatoid arthritis.

What it does:

In rheumatoid arthritis, the immune system (body's defenses against infection and foreign substances) turns against a patient's own joint tissue. This causes inflammation and the patient can have pain, stiffness, and swelling, which over many months can lead to deformities of the joints.

ARAVA works in rheumatoid arthritis by reducing or suppressing to a certain extent the abnormal activation and multiplication of cells responsible for the inflammation.

From the results of studies in patients with rheumatoid arthritis you can expect ARAVA to reduce your arthritis signs and symptoms. It may take about 4 weeks until you start to feel an improvement in your symptoms.

When it should not be used:

Tell your doctor and do not start treatment with ARAVA:

- if you suspect that you may be pregnant, you must inform your doctor and you must not start taking ARAVA. ARAVA may increase the risk of having a baby with a birth defect.
- if you are of childbearing age, it must be confirmed with a pregnancy test that you are not pregnant just before you begin treatment with ARAVA. There is also a risk that male patients taking ARAVA might father a deformed baby. Both male and female patients should read below in the WARNINGS AND PRECAUTIONS section **"What are the risks of birth defects with ARAVA?"**
- if you have a disease of the liver. Otherwise, your disease may get worse;
- if you have ever had an allergic reaction to leflunomide (especially a serious skin reaction, for example red rash, skin peeling, blisters), to teriflunomide, or to any of the other ingredients (see below **"What the nonmedicinal ingredients are:"**);
- if you suffer from a disease (for example, AIDS) which decreases the strength of your body's defenses against infection. Otherwise the weakening of your body's defenses against infection worsen;
- if your bone marrow does not work well or if the number of red cells, white cells, or platelets in your blood is very much decreased. Again ARAVA could worsen this problem;
- if you are suffering from a serious infection, as your infection may be more difficult to treat;
- if you have a disease of the kidney, because the kidney plays a role in the elimination of ARAVA.
- if you are nursing your baby, as ARAVA passes into breast milk and its effect on the nursing infant are not known;
- 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.

What the medicinal ingredient is:

The tablets contain the active drug, leflunomide.

What the nonmedicinal ingredients are:

Lactose monohydrate

The other nonmedicinal ingredients are: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, maize starch, talc, titanium dioxide, yellow ferric oxide (20 mg tablet only)

What dosage forms it comes in:

ARAVA comes as tablets of 3 different strengths:

I. a 100 mg white round tablet with 'ZBP' code on one side;
II. a 20 mg light yellow triangular tablet with 'ZBO' code on one side;
III. a 10 mg white round tablet with 'ZBN' code on one side.

WARNINGS AND PRECAUTIONS

The medication can stay in your body for a long period of time. Therefore some precautions and side effects may follow from this characteristic of the drug.

WHAT ARE THE RISKS OF BIRTH DEFECTS WITH ARAVA?

For female patients:

You may be at high risk of having a deformed baby if you do not follow the following instructions:

If you are pregnant, or suspect that you may be, you must tell your doctor and you must not start taking ARAVA.

If you are of childbearing age (women who might get pregnant), it must be confirmed with a pregnancy test that you are not pregnant just before beginning your treatment.

Women must use reliable birth control methods when taking ARAVA. If you are of childbearing age, discuss methods to avoid becoming pregnant with your doctor.

The risk of giving birth to a deformed baby can best be estimated by the amount of ARAVA remaining in your body when you become pregnant. If you plan to become pregnant after stopping ARAVA, it is important to inform your doctor beforehand. Once you stop taking ARAVA, you must wait a period of 2 years before trying to get pregnant. However, this waiting period may be shortened to a few weeks by taking a certain medicine that will speed up the elimination of ARAVA from your body. If this option is chosen, inform your doctor if you are taking an oral contraceptive pill. The medicine that speeds up the elimination of ARAVA may lower the effect of your contraceptive pill and you may need another contraceptive method during this period. In either case it should be confirmed by two blood tests two weeks apart that ARAVA has been sufficiently eliminated from your body before you try to become pregnant. Your doctor can give you more information about the options available to reach low blood levels of ARAVA. For information regarding blood levels measurements, please also contact your doctor.

If you are currently taking ARAVA, or if you have taken it within the last 2 years and you believe that you may be pregnant, it is VERY IMPORTANT that you contact your doctor immediately. You must have a pregnancy test at the first delay of your period, and 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 your period to rapidly start the treatment which speeds up elimination of ARAVA from the body, as this may decrease the risk to your baby.

For male patients:

You may be at high risk of fathering a deformed baby if you do not follow the following instructions:

Once you start taking ARAVA, you should take every precaution to avoid getting your partner pregnant. You should use a reliable birth control as recommended by your doctor, during ARAVA therapy. If you have any questions about reliable birth control methods, consult your doctor.

If you wish to father a child after having stopped ARAVA, it is important to inform your doctor beforehand. Once you stop taking ARAVA, you must wait a period of 2 years before trying to father a child. However, this waiting period may be shortened to a few weeks by taking a certain medicine that will speed up the elimination of ARAVA from your body. In either case it should be confirmed by two blood tests that ARAVA has been sufficiently eliminated from your body and you should then wait for another 3 months before you try to get your partner pregnant. Your doctor can give you more information about the options available to reach low blood levels of ARAVA. For information regarding blood level measurements, please also contact your doctor.

If you are currently taking ARAVA, or if you have taken it within the last 2 years and your partner suspects that she may be pregnant you must both immediately contact your doctors. Your partner must have a pregnancy test at the first delay of her period, and if the test confirms that she is pregnant, you should discuss with your doctors the risk of the treatment to the baby.

WHAT ARE OTHER PRECAUTIONS WITH ARAVA?

All patients:

Before you start to take ARAVA, and also while you are 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. It is important to keep your medical appointments.

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 if you have, or if you have had heart disease or lung disorders.

Tell your doctor if you have unexplained chronic diarrhea or weight loss.

In certain circumstances (serious side effects, changing antirheumatic treatment or in case of a desired pregnancy) your doctor will decide that you should take a certain medicine which speeds up the elimination of ARAVA from your body.

Tell your doctor if you experience symptoms that can cause numbness, tingling or burning in the hands and feet, muscle weakness or other altered sensations while taking ARAVA. Your doctor will give you a medication which can speed up the elimination of ARAVA from your body.

INTERACTIONS WITH THIS MEDICATION

Drinking alcohol with ARAVA:
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.

Taking other medicines together with ARAVA:
Medication to relieve pain and inflammation such as nonsteroidal anti-inflammatory drugs (NSAIDs) or cortisone can be taken together with ARAVA. However, your doctor will give you specific instructions about these medicines.

You must not receive any type of live vaccinations while treated with ARAVA or within 6 months after stopping ARAVA. Check ahead with the clinic if you have to be vaccinated.

Before you start taking ARAVA, be sure to tell your doctor about **all** medicines you are taking or have taken recently including any that you bought without a prescription or any natural products. This is because the effects of ARAVA or the other medicines may be changed or you might get side effects. Furthermore, do not start any new medicine, whether prescription, non-prescription or natural products without first checking with your doctor.

Examples of drugs that may interact with ARAVA are:

- activated charcoal
- azathioprine
- cholestyramine
- cimetidine (stomach acid medicine)
- D penicillamine
- duloxetine (anti-depressant)
- gold
- methotrexate
- phenytoin
- teriflunomide
- theophylline (asthma medicine)
- tizanidine (muscle relaxant medicine)
- warfarin
- medicines used to treat diabetes, such as: repaglinide, pioglitazone, rosiglitazone, nateglinide or tolbutamide
- oral contraceptives
- some medicines used to treat infections such as: antimalarial drugs, cefaclor, ciprofloxacin, penicillin G, rifampin, rifampicin, zidovudine
- medicines used to lower blood cholesterol, such as: rosuvastatin, atorvastatin, simvastatin, pravastatin
- anti-inflammatory drugs, such as: indomethacin, ketoprofen, sulfasalazine
- diuretics (water losing pills), such as: furosemide
- some medicines to treat cancer such as: paclitaxel, methotrexate, topotecan, daunorubicin, doxorubicin

ARAVA can stay in your body for a long period of time after you stop taking it. Therefore, when ARAVA is stopped and another drug (for example methotrexate) is started to treat your rheumatoid arthritis, there is a possibility of increased risks of adverse events. Your doctor may give you a certain medicine that will speed up the elimination of ARAVA from your body before starting the other drug.

PROPER USE OF THIS MEDICATION

Usual dose:

ARAVA has been prescribed for you alone. Do not share it with anyone else, even if their symptoms are the same as yours, as it may bring more harm than good.

ARAVA is supplied as film-coated tablets of 10, 20, and 100 mg strengths. Your doctor will usually want you to build up the amount of ARAVA in your body. For doing so, you will usually start the treatment by taking a tablet of 100 mg once daily for the first 3 days. Thereafter, your doctor will usually reduce the dose to a tablet of 20 mg to be taken once daily. For some people, their doctor will instead prescribe a tablet of 10 mg once daily.

You should always follow your doctor's instructions. Do not take any more or any less tablets than what your doctor says. You will normally take ARAVA over long periods of time. However, your doctor will advise you if and when you need to stop taking ARAVA.

You can take ARAVA during meals or at any time between meals. However, it works best if you take it at the same time every day. Swallow the tablet whole with a glass of water or another fluid.

Overdose:

If you accidentally take more than one tablet, nothing is likely to happen. 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 AND WHAT TO DO ABOUT THEM". Should this happen, it is possible that medicine may be administered by your doctor in order to speed up the elimination of ARAVA from your body.

In case of drug overdose, contact a heath care practitioner, hospital emergency department or Regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a tablet of ARAVA 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with any medication, ARAVA can cause some side effects. It

may, however, affect different people in different ways. Just because side effects have occurred in other people does not mean you will get them. In studies of patients with rheumatoid arthritis, common side effects included: diarrhea, loss of appetite, nausea (queasiness), vomiting, abdominal pain, weight loss (usually mild), headache, dizziness, weakness, abnormal skin sensations like tingling, inflammation of a tendon sheath, increased hair loss, eczema, and dry skin. Should these side effects occur and be bothersome, please consult your doctor. Your doctor may decide to decrease the dose of ARAVA or may want you to stop the medication.

ARAVA can also increase blood pressure (usually mildly) and your blood pressure will need to be checked regularly.

Ulceration or inflammation of the mouth and skin rash are common with ARAVA. However, 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 cases, such reactions may develop into severe, sometimes life-threatening skin reactions such as painful blister, red rash spreading and skin peeling**. They may, therefore, require discontinuation of ARAVA and immediate action by your doctor.

Also common are mild allergic reactions 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, do not take any more ARAVA tablets and consult your doctor immediately.

Blood tests may often show a decrease in the number of white blood cells. However, a pronounced decrease in the number of white cells or of all blood cells may occur rarely in some patients. Tell your doctor without any delay if you have symptoms such as paleness, tiredness, if you bruise or bleed easily or if you have symptoms of infection such as fever, chills or sore throat. Such symptoms may be due to disorders of your blood cells. They may require discontinuation of ARAVA and other medications, and further action by your doctor.

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

Like other antirheumatic medicines that to some extent reduce the immune defense, ARAVA may increase the susceptibility to infections. Tell your doctor without any delay if you have any symptoms of an infection (such as fever, sore throat, or cough). This is because some infections might become more severe and, therefore, they need to be treated early.

Cases of lung inflammation causing difficulty breathing have occurred rarely in patients receiving ARAVA. Tell your doctor without delay if you experience new or worsening of shortness of breath and/or cough, with or without associated fever, at any time while you are taking ARAVA.

Your doctor will assess your condition and will decide on appropriate course of action. This may require additional tests, for example, blood analysis. In some cases your doctor may recommend to stop taking ARAVA. However, simply stopping ARAVA may not be enough to prevent further progression of the side effect. You may be required to take certain medicines, which speeds up the elimination of ARAVA from you body. Additional follow-up visits to the doctor and diagnostic tests may be needed to monitor your condition.

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, do not take any more ARAVA tablets and consult your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
	Only if severe	**In all cases**	
Common			
Hypertension (high blood pressure)		√	
Pain and swelling of the tendon	√		
Loss of appetite	√		
Skin rash			√
Mouth sores		√	
Uncommon			
Bruise or bleed easily		√	
Heart disorders (for example: chest pain, palpitation, fast heart beat)		√	
Eye disorders (for example: dimness of vision, eye infection, cataract)		√	
Infection or symptoms of infection such as fever (see text)		√	
Liver problem, if symptoms such as jaundice or other related symptoms (see text)			√
Lung inflammation, if symptoms such as new or worsening of shortness of breath or other related symptoms (see text)		√	
Severe allergic reactions			√
Unknown frequency			
Colitis: abdominal pain, bloody stools, diarrhea, fever, rectal pain, bloating, weight loss		√	
Shortness of breath, fatigue, dizziness, chest pain		√	

This is not a complete list of side effects. For any unexpected effects while taking* ARAVA*, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at: www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Do not expose ARAVA tablets to light. Store this medicine at temperatures between 15 ºC and 30 ºC, in a dry place. As with all medicines, you should keep ARAVA tablets out of the reach of children. Do not use the tablets in this package after the expiry date shown on the container label.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.sanofi.ca, or by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-800-265-7927.

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