PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Arava 10 mg, Arava 20 mg, Film-coated Tablets

SANOFI

Active ingredient:

Each film-coated Arava 10 mg tablet contains: Leflunomide 10 mg

Each film-coated Arava 20 mg tablet contains: Leflunomide 20 mg

Inactive ingredients: See section 2 'Before using the medicine' and section 6 'Further Information'.

Read the leaflet carefully in its entirety before using the medicine.

This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

In addition to the leaflet, the Arava preparation is provided with a Patient Safety Information Card. This card contains important safety information that you must know and abide by before starting and during treatment with Arava. You must read the Patient Safety Information Card and patient leaflet before starting to use the preparation. Keep the card for further reference if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Arava belongs to a group of medicines called anti-rheumatic medicines. It contains the active ingredient leflunomide.

Arava is used to treat adults with active rheumatoid arthritis, to slow progression of the disease and to improve physical functioning, or to treat active psoriatic arthritis.

Therapeutic group: Selective immune system suppressors.

Symptoms of rheumatoid arthritis include: joint inflammation, swelling, difficulty moving and pain. Other symptoms that affect the entire body include: loss of appetite, fever, reduced energy and anemia (red blood cell deficiency).

Symptoms of active psoriatic arthritis include: joint inflammation, swelling, difficulty moving, pain and red scaly patches on the skin (skin lesions).

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient, you have ever had an **allergic** reaction to leflunomide (especially a severe skin reaction, often accompanied by fever, joint pain, red skin patches or blisters, e.g., Stevens-Johnson syndrome) or to any of the additional ingredients contained in the medicine (see section 6 'Further Information'), or if you are allergic to teriflunomide (used to treat multiple sclerosis),
- You have any **liver problems**,
- You have moderate to severe **kidney problems**,
- You have a very low amount of **proteins in the blood** (hypoproteinaemia),
- You suffer from any problem that affects your **immune system** (e.g., AIDS),
- You have a problem with the **bone marrow**, or a low red or white blood cell count or a reduced number of blood platelets,
- You are suffering from a **serious infection**,
- You are **pregnant**, think you may be pregnant, or are breastfeeding.

Special warnings regarding use of the medicine

Before treatment with Arava, tell the doctor if:

- You have ever suffered from an **inflammation of the lung** called **interstitial lung disease**.
- You have ever had **tuberculosis** or if you have been in close contact with a person who has or has had tuberculosis in the past. Your doctor may perform tests to see if you have tuberculosis (see 'Tests and follow-up' section).
- You are **male** and wish to father a child.

  As the possibility that Arava passes into semen cannot be ruled out, reliable contraceptive measures should be used during treatment with Arava.
- A man who plans to father a child should refer to a doctor, who may advise him to stop taking Arava and to take certain medicines to rapidly and sufficiently clear Arava from his body. Afterwards, he will have to perform a blood test to ensure that Arava was sufficiently cleared from his body, and then wait at least another 3 months before attempting to father a child.
- You are due to undergo a certain blood test (calcium level). The result may falsely indicate low calcium levels.

Arava can occasionally cause certain problems in the blood, liver, lungs or nerves of the arms or legs. It may also cause several severe allergic reactions (including DRESS – drug reaction with eosinophilia and systemic symptoms) or increase the risk of acute infection. For further information, see section 4 'Side Effects'.

DRESS is a reaction initially characterized by flu-like symptoms and facial rash, and later by a more extensive rash with high fever, increased liver enzyme levels in the blood, increased eosinophil-type white blood cells and swollen lymph nodes.

Refer to your doctor if you have unexplained chronic diarrhea. The doctor may perform additional tests.

Refer to your doctor if you develop a skin ulcer during the course of treatment with Arava (also see section 4 'Side effects').

Children and adolescents

Arava is not intended for use in children and adolescents under the age of 18.

Tests and follow-up

Before starting and during treatment with the medicine, the doctor will refer you for blood and liver function tests.

Before starting treatment, an evaluation for presence of active or inactive tuberculosis should be performed.

Patients who suffered in the past from tuberculosis must be under tight surveillance due to the possibility of tuberculosis becoming active again.

During the course of treatment, the doctor will also refer you for blood pressure tests since the medicine may increase blood pressure.

If you are taking warfarin or other oral medicines (used to thin the blood) concomitantly with Arava treatment, your INR (International Normalised Ratio) must be strictly monitored.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Especially if you are taking:

- Other medicines to treat rheumatoid arthritis, such as antimalarials (e.g., chloroquine and hydroxychloroquine), gold injected intramuscularly or taken orally, D-penicillamine, azathioprine and other immunosuppressive medicines (e.g., methotrexate), as these combinations are not advisable,
- Warfarin and other oral medicines used to thin the blood, for which monitoring is necessary in order to reduce the risk of their side effects,
- Teriflunomide (for multiple sclerosis),
- Repaglinide, pioglitazone, nateglinide or rosiglitazone (for diabetes)',
- Daunorubicin, doxorubicin, paclitaxel or topotecan (for cancer),
- Duloxetine (for depression, urinary incontinence or kidney disease in diabetics),
- Alosetron (to treat acute diarrhea),
- Theophylline (for asthma),
- Tizanidine (a muscle relaxant),
- Oral contraceptives (that contain ethinylestradiol and levonorgestrel),
- Cefaclor, benzylpenicillin (penicillin G), ciprofloxacin (for infections),
- Indomethacin, ketoprofen (for pain or inflammation),
- Furosemide (a diuretic agent, for heart disease),
- Zidovudine (for HIV infection),
- Rosuvastatin, simvastatin, atorvastatin, pravastatin (for high cholesterol),
- Sulfasalazine (for inflammatory bowel disease or rheumatoid arthritis),
- Cholestyramine (to lower cholesterol) or activate charcoal, as these medicines may lower the amount of Arava that is absorbed into the body.

If you are already taking a non-steroidal anti-inflammatory drug (NSAID) and/or corticosteroids, you may continue taking them after commencing treatment with Arava.

Vaccinations

If you have to be vaccinated, consult with the doctor. Certain vaccinations cannot be given during the treatment with Arava and for some time after stopping treatment with Arava.

Use of the medicine and food

The medicine can be taken with or without food.

Use of the medicine and alcohol consumption

It is not recommended to drink alcohol during the treatment with the medicine. Drinking alcohol during the treatment with the medicine may increase the risk of liver damage.

Pregnancy and breastfeeding

Do not use the medicine when you are **pregnant** or think you are **pregnant**. If you are pregnant or become pregnant during the course of treatment with the medicine, the risk of delivering a baby with severe congenital defects increases. Women of childbearing potential must not take Arava without using reliable contraceptive measures.

Consult with the doctor if you plan to become pregnant after stopping treatment with Arava, since you must ensure that all traces of the medicine have cleared from your body before you try to become pregnant. This period can last up to two years. This may be reduced to a few weeks by taking certain medicines that accelerate the clearance of Arava from your body.

In any case, you should perform a blood test to ensure that Arava has sufficiently cleared from your body and then wait at least another month before becoming pregnant.

For further information about the laboratory tests, refer to your doctor.

If you suspect that you have become pregnant during the treatment with Arava or during the two years after stopping treatment with Arava, refer to a doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, the doctor may suggest treatment with certain medicines to clear Arava rapidly and sufficiently from your body to reduce the risk to the baby.

Do not take Arava when **breastfeeding**, since the medicine passes into breast milk.

Driving and operating machinery

Do not drive or operate dangerous machinery while using the medicine, since this medicine may cause you to feel dizzy, which may impair your ability to concentrate and respond.

Important information about some of the ingredients of the medicine

The tablets contain **lactose**. If you have an intolerance to certain sugars, refer to the doctor before commencing treatment.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

The usual starting dosage is generally one dose of 100 mg, once a day, for 3 days. Afterwards, most patients need a dosage of:

- For rheumatoid arthritis: 10 or 20 mg, once a day, depending on the severity of the disease.
- For psoriatic arthritis: 20 mg, once a day.

Do not exceed the recommended dose.

Swallow the tablet **whole** with a lot of **water**.

There is no information regarding crushing/halving/chewing the tablet.

If you accidentally took a higher dosage, refer to a doctor and bring the package of the medicine with you.

If you took an overdose or if a child has accidentally swallowed the medicine, immediately refer to a doctor or hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine at the required time, take a dose as soon as you remember, unless it is almost time for the next dose.

Do not take a double dose to compensate for a forgotten dose.

Adhere to the treatment regimen as recommended by the doctor. Four or more weeks may pass until you begin to feel an improvement in your condition.

Some patients will experience an additional improvement after 4-6 months of treatment.

Usually, the treatment with Arava lasts for a long period of time.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Arava may cause side effects in some users.

Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Discontinue use and refer to a doctor immediately if:

- You experience **weakness**, feel dizzy or have **difficulty breathing**, since these may be signs of a severe allergic reaction,
- You develop a **skin rash** or **mouth ulcers**, as these may be indicative of severe, sometimes life-threatening reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS). See section 2.

Refer to the doctor immediately if one of the following side effects occur:

- **Pale skin, tiredness** or **bruising,** since these can be indicative of blood disorders caused by an imbalance in different types of blood cells,
- **Tiredness, abdominal pain** or **jaundice** (yellowing of the eyes or skin), since these may be indicative of severe conditions such as liver failure, that may be fatal,
- Symptoms of **infection**, such as **fever, sore throat** or **cough**, as this medicine may increase the risk of severe infection, which may be life-threatening,
- **Cough** or **breathing problems**, as these may be indicative of lung problems (interstitial lung disease or pulmonary hypertension),
- **Unusual tingling**, **weakness** or **pain in the palms of the hands or feet**, as these may be indicative of nervous system problems (peripheral neuropathy).

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

- A slight decrease in the number of white blood cells (leucopenia),
- Mild allergic reactions,
- Lack of appetite, weight loss (usually insignificant),
- Tiredness (asthenia),
- Headache, dizziness,
- Abnormal sensations in the skin, such as tingling (paraesthesia),
- Mild increase in blood pressure,
- Colitis,
- Diarrhea,
- Nausea, vomiting,
- Inflammation or ulcers in the mouth,
- Abdominal pain,
- Increase in some liver function test results,
- Increased hair loss,
- Eczema, dry skin, rash, itching,
- Tendonitis (pain in the tendons caused by inflammation of the membrane surrounding the tendons, usually in the palms of the hands or feet),
- Increase in certain enzymes in the blood (creatine phosphokinase),
- Problem with the nerves of the hands or legs (peripheral neuropathy).

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

- Decreased number of red blood cells (anemia) and decreased number of blood platelets (thrombocytopenia),
- Decreased blood potassium level,
- Anxiety,
- Taste disturbances,
- Urticaria (nettle rash),
- Tendon rupture,
- Increased blood fat levels (cholesterol and triglycerides),
- Decreased blood phosphate levels.

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

- Increased number of eosinophilic blood cells (eosinophilia); mildly decreased number of white blood cells (leucopenia), decreased number of all blood cells (pancytopenia),
- Severe increase in blood pressure,
- Inflammation of the lung (interstitial lung disease),
- Increase in liver function test results, which may develop into severe conditions, such as hepatitis and jaundice,
- Severe infections called sepsis, that may be fatal,
- Increase of certain enzymes in the blood (lactate dehydrogenase).

Very rare side effects (may affect up to 1 in 10,000 patients)

- A marked decrease in white blood cells (agranulocytosis),
- Severe and potentially severe allergic reactions,
- Inflammation of blood vessels (vasculitis, including cutaneous necrotizing vasculitis),
- Inflammation of the pancreas (pancreatitis),
- Severe liver injury, such as liver failure or necrosis, that may be fatal,
- Severe, sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).

Other side effects, such as kidney failure, a decrease in the level of uric acid in the blood, pulmonary hypertension, impaired male fertility (which is reversible upon stopping treatment with the medicine), cutaneous lupus (characterized by rash/erythema on skin areas that are exposed to light), psoriasis (new or worsened), or a severe allergic reaction to the medicine called DRESS (see section 2, 'Special warnings regarding use of the medicine') and skin ulcer (round, open sore in the skin through which the underlying tissues can be seen) may also occur at an unknown frequency.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning.

Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp. date) that appears on the package.

The expiry date refers to the last day of that month.

Storage conditions

Store below 25°C; keep the bottle tightly closed.

Do not discard the medicine in the wastewater or household waste. Consult the pharmacist about how to dispose of the medicine. This will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:

Tablet core: Lactose monohydrate, maize starch, crospovidone, polyvidone K25, colloidal anhydrous silica, magnesium stearate.

Film coating: Methylhydroxypropylcellulose 5mPs, titanium dioxide (E171), talc, macrogol 8000.

Arava 20 mg also contains: yellow ferric oxide (E172).

Each 10 mg tablet contains 78 mg lactose monohydrate.

Each 20 mg tablet contains 72 mg lactose monohydrate.

What the medicine looks like and the contents of the package:

Arava 10 mg film-coated tablets are white and round. ZBN is imprinted on one side. The tablets are packaged in a bottle of 30 or 100 tablets.

Arava 20 mg film-coated tablets are yellowish and triangular. ZBO is imprinted on one side. The tablets are packaged in a bottle of 30 or 100 tablets.

Not all package sizes may be marketed.

License holder and Importer and its address: sanofi-aventis Israel ltd., 10 Beni Gaon Street, P.O.B. 8090, Netanya, Israel.

Revised in June 2022 according to MOH guidelines.

This leaflet does not contain all the information about the preparation. If you have any questions or are not sure about something, please refer to the doctor.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Arava 10 mg: 121-78-30132
Arava 20 mg: 121-79-30133

ARAVA-PIL-22.0