PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only.

Sandimmun® Concentrate for Solution for Infusion, 50 mg/ml

Active ingredient:
Ciclosporin 50 mg/ml

Inactive and allergenic ingredients in the preparation: see section 6 "Further information" and the paragraph "Important information about some of the ingredients of the medicine" in section 2.

Read this 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 to treat you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

The name of your medicine is Sandimmun Concentrate for Solution for Infusion. It contains the active ingredient ciclosporin.
The concentrated solution is used to prepare a solution which is administered by intravenous infusion. The medicine belongs to a group of medicines known as immunosuppressants. These medicines are used to reduce the reaction of the body's immune system.
- Sandimmun in combination with corticosteroids is intended to prevent rejection of a transplanted organ following a kidney, liver or heart transplantation.
- The medicine may also be used to treat chronic transplant rejection in patients previously treated with other immunosuppressants.
- Bone marrow transplantation.

Sandimmun is used to control the body's immune system following an organ transplant, including bone marrow transplantation. Sandimmun prevents rejection of transplanted organs by blocking the development of certain cells which would normally attack the transplanted organ.

Therapeutic group: Immunosuppressants.

2. BEFORE USING THE MEDICINE

Sandimmun will only be prescribed for you by a doctor with experience in transplants. Follow all the doctor's instructions carefully. The instructions may differ from the general information contained in this leaflet.

Do not use the medicine:
- if you are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine (see section 6 "Further information" as well as section "Important information about some of the ingredients of the medicine" regarding castor oil and ethanol).
- with preparations containing Hypericum perforatum (*Hypericum perforatum*, St. John´s Wort).
- with preparations containing dabigatran etexilate (used to prevent blood clots after surgery) or bosentan and aliskiren (used to reduce high blood pressure).

If the sections listed above apply to you, do not use Sandimmun **and tell the doctor**. If you are not sure, talk to the doctor or pharmacist before taking the medicine.

Special warnings regarding use of the medicine

Before and during treatment with Sandimmun, tell the doctor immediately if:
- you have any signs of infection, such as fever or a sore throat. Sandimmun suppresses the immune system and may also affect your body's ability to fight infection.
- you have liver problems.
- you have kidney problems. Your doctor will carry out regular blood tests and may change the dosage, as necessary.
- you develop high blood pressure. Your doctor will check your blood pressure regularly and may give you a medicine to lower blood pressure, as necessary.
- you have low levels of magnesium in your body. Your doctor may give you magnesium supplements to take, especially just after your transplant operation.
- you have high blood potassium levels.
- you have gout.
- you need to receive a vaccination.

If one or more of the sections listed above apply to you before or during treatment with Sandimmun, tell your doctor immediately.

Sunlight and sun protection
Sandimmun suppresses your immune system, and thereby increases your risk of developing types of cancer, particularly cancer of the skin and lymphoid system. You should limit your exposure to sunlight and UV light by:
- wearing appropriate protective clothing.
- frequently using sunscreens with a high protection factor.

Talk to your doctor before taking Sandimmun:
- if you have or have had alcohol dependence-related problems.
- if you have epilepsy.
- if you have any liver problems.
- if you are pregnant.
- if you are breastfeeding.
- if this medicine is being given to a child.

If one or more of these sections apply to you (or you are not sure), tell your doctor before using Sandimmun.
This is because this medicine contains alcohol (see paragraph "Important information about some of the ingredients of the medicine" regarding castor oil and ethanol).

Tests and follow-up
Monitoring during your treatment with Sandimmun:
Your doctor will check:
- the **levels of ciclosporin in your blood**, especially if you have had a transplant.
- your **blood pressure** before the start of treatment and regularly during treatment.
- your **liver and kidney** functions.
- your **blood fat** levels.

If you have further questions about how Sandimmun works or why this medicine has been prescribed for you, ask your doctor.

Children and adolescents:
There is limited experience with Sandimmun treatment in children.

Elderly (65 years of age and older)
There is limited experience with Sandimmun in elderly patients. Your doctor will monitor your kidney functions.

Drug interactions:
If you are taking, or have recently taken, or might take, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular if you are taking any of the following medicines before or during Sandimmun treatment:
- Medicines that may affect your potassium levels. These medicines include medicines which contain potassium, potassium supplements, potassium-sparing diuretics, and some medicines that lower your blood pressure.
- Methotrexate. This medicine is used to treat tumors, severe psoriasis and severe rheumatoid arthritis.
- Medicines which may increase or decrease the level of ciclosporin (the active ingredient in Sandimmun) in your blood. The doctor might check the level of ciclosporin in your blood when starting or stopping treatment with other medicines.
  - Medicines which may increase the level of ciclosporin in your blood. These medicines include: antibiotics (such as erythromycin or azithromycin), anti-fungals (voriconazole, itraconazole), medicines for heart problems or high blood pressure (diltiazem, nicardipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral contraceptives, danazol (to treat menstrual problems), medicines to treat gout (allopurinol), cholic acid and its derivatives (to treat gallstones), protease inhibitors to treat the human immunodeficiency virus (AIDS), imatinib (to treat leukemia or tumors), colchicine, telaprevir (to treat hepatitis C), cannabidiol (uses amongst others include treatment of seizures).
  - Medicines which may decrease the level of ciclosporin in your blood. These medicines include: barbiturates (medicines used as hypnotics), some anti-convulsants (such as carbamazepine or phenytoin), octreotide (to treat acromegaly or neuroendocrine tumors in the gut), anti-bacterial medicines used to treat tuberculosis, orlistat (to help weight loss), herbal medicines containing St. John's wort (Hypericum perforatum), ticlopidine (used after a stroke), certain medicines which lower blood pressure (bosentan), and terbinafine (an anti-fungal medicine used to treat infections of the toes and nails).
- Medicines which may affect your kidneys. These medicines include: anti-bacterial medicines (gentamicin, tobramycin, ciprofloxacin), anti-fungal medicines which contain amphotericin B, medicines for urinary tract infections which contain trimethoprim, medicines for cancer which contain melphalan, medicines used to reduce the amount of acid in your stomach (acid secretion inhibitors of the H2-receptor antagonist type), tacrolimus, pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibric acid (to lower the fat levels in the blood).
- Nifedipine. This medicine is used to treat high blood pressure and angina pectoris. You might get swollen gums that might grow over your teeth if you are taking nifedipine during your treatment with ciclosporin.
- Digoxin (to treat heart problems), medicines which reduce cholesterol (HMG-CoA reductase inhibitors, which also called statins), prednisolone, etoposide (to treat cancer), repaglinide (an anti-diabetic medicine), immunosuppressants (everolimus, sirolimus), ambrisentan and specific anti-cancer medicines called anthracyclines (such as doxorubicin).

If one or more of the aforementioned apply to you (or you are not sure), talk to your doctor or pharmacist before using Sandimmun.

Use of Sandimmun with food and drink:
Do not take Sandimmun with grapefruits or grapefruit juice. This is because these can affect the way Sandimmun works.

Pregnancy and breastfeeding:
Consult your doctor or pharmacist before using this medicine. Your doctor will discuss with you the potential risks of taking Sandimmun during pregnancy.
- **Tell your doctor if you are pregnant or planning a pregnancy.** Experience with Sandimmun in pregnancy is limited. In general, Sandimmun should not be taken during pregnancy. If it is necessary for you to take the medicine, your doctor will discuss with you the benefits and potential risks of taking this medicine during pregnancy.
- **Tell your doctor if you are breastfeeding.** Breastfeeding is not recommended during treatment with Sandimmun. This is because ciclosporin, the active ingredient, passes into breast milk. This may affect your baby.

Hepatitis C:
Tell your doctor if you have hepatitis C. Your liver functions may change while under hepatitis C treatment, which may affect the ciclopsorin levels in your blood. Your doctor may have to closely monitor the ciclosporin levels in your blood and adjust the dosage after you start treatment for hepatitis C.

Driving and operating machinery:
Sandimmun contains alcohol. This may affect your ability to drive and operate machinery.
Regarding children, caution them against riding a bicycle or playing near the street and the like.

Important information about some of the ingredients of the medicine:
Sandimmun contains castor oil and ethanol
Sandimmun contains castor oil which may cause severe allergic reactions.
Sandimmun contains 278 mg of ethanol (alcohol) per ml, which is equivalent to 34.4 % v/v . A 100 mg dose of Sandimmun contains 556 mg ethanol. This amount is equivalent to approximately 14 ml of beer or 6 ml of wine. This small amount of alcohol does not have any noticeable effect.

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.
Your doctor will work out the correct dosage of Sandimmun for you. This depends on your body weight and the reason you are being given the medicine.
The usual dosage is generally:
- The total dosage each day is usually between 3-5 mg per kilogram of your weight. This amount is divided into two doses.
- Usually, a higher dosage is used immediately after your transplant. A lower dosage is used once your transplanted organ or bone marrow has stabilized.
- Your doctor will adjust your dosage to one that is ideal for you. To do this, your doctor may need to perform several blood tests.

How Sandimmun is used
The medicine will be diluted before use, at a ratio of 1:20 to 1:100, with saline solution or 5% glucose and then be given to you by slow infusion over 2-6 hours. The diluted medicine must be thrown away after 24 hours.

Duration of Sandimmun treatment
You will be switched to ciclosporin in the form of capsules or oral solution (both forms are intended for oral ingestion) as soon as possible.
Detailed instructions about how to use Sandimmun are provided in English at the end of the leaflet, in section "Instructions for healthcare professionals on how to prepare and administer the preparation".

If you have been given a higher dosage of Sandimmun than required
Too much of the medicine may affect your kidneys. You will undergo routine blood tests and routine hospital visits. This will give you the chance to talk to your doctor about the treatment and talk about any problems you may be experiencing.
If you think you have been given too much Sandimmun, tell your doctor immediately.

Do not exceed the recommended dose.

Adhere to the treatment regimen as recommended by the doctor.

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

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

4. SIDE EFFECTS

As with any medicine, use of Sandimmun may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Some side effects could be serious.
Tell your doctor immediately if you notice any of the following serious side effects:
- Signs of anaphylactic reactions that appear after intravenous administration of Sandimmun. These reactions can consist of flushing of the face and the upper chest, fluid in the lungs, shortness of breath, wheezing, blood pressure changes (you may feel like you are about to faint) and accelerated heartbeat.
- Like other medicines that act on the immune system, ciclosporin may influence your body's ability to fight infections and may cause tumors or other cancers, particularly of the skin. Signs of infection might be fever or sore throat.
- Changes in your vision, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others are saying, and muscle weakness. These might be signs of an infection of the brain called progressive multifocal leukoencephalopathy (PML).
- Brain problems with signs such as seizures, confusion, disorientation, reduced responsiveness, personality changes, feeling agitated, sleeplessness, vision disturbances, blindness, coma, paralysis of part or all of the body, stiff neck, loss of coordination with or without abnormal speech or eye movements.
- Swelling of the back part of the eye. This may be associated with blurred vision and may also affect your eyesight because of the increased pressure inside your head (benign intracranial hypertension).
- Liver problems and damage, with or without yellow skin and eyes, nausea, loss of appetite and dark urine.
- Kidney problems, which may greatly reduce the amount of urine you produce.
- Low level of red blood cells or platelets. The signs include pale skin, tiredness, breathlessness, dark urine (a sign of breakdown of red blood cells), bruising or bleeding for no apparent reason, confusion, disorientation, decreased alertness and kidney problems.

Additional side effects include:

Very common side effects (occur in more than 1 in 10 users):
- Kidney problems.
- High blood pressure.
- Headache.
- Uncontrollable shaking of your body.
- Excessive growth of body and facial hair.
- High level of lipids in your blood.

If any of the effects listed above affects you severely, **tell the doctor**.

Common side effects (occur in 1-10 in 100 users):
- Seizures.
- Liver problems.
- High levels of sugar in your blood.
- Tiredness.
- Loss of appetite.
- Nausea, vomiting, abdominal pain/abdominal discomfort, diarrhea.
- Excessive hair growth.
- Acne, hot flushes.
- High fever.
- Low level of white blood cells.
- Numbness or tingling.
- Muscle pain, muscle spasms.
- Stomach ulcer.
- Gum tissue overgrowth, until the teeth are covered by the tissue.
- High level of uric acid or potassium in your blood, low levels of magnesium in your blood.

If any of the effects listed above affects you severely, **tell the doctor**.

Uncommon side effects (effects that occur in 1-10 in 1,000 users):
- Symptoms of brain disorders including sudden fits, mental confusion, sleeplessness, disorientation, eyesight disturbance, loss of consciousness, sense of weakness in the limbs, impaired movements.
- Rash.
- General swelling.
- Weight gain.
- Low level of red blood cells, low level of platelets in the blood which could increase the risk of bleeding.

If any of the side effects listed above affects you severely, **tell the doctor**.

Rare side effects (effects that occur in 1-10 in 10,000 users):
- Nerve disturbance with numb or tingling sensation in the fingers and toes.
- Inflammation of the pancreas with severe upper abdominal pain.
- Muscle weakness, loss of muscle strength, pain in muscles of the legs or hands or anywhere else in the body.
- Destruction of red blood cells that involve kidney problems with symptoms such as swelling of the face, abdomen, hands and/or feet, reduction in urination, difficulty breathing, chest pain, convulsions, loss of consciousness.
- Changes in menstrual cycle, chest enlargement in men.

If any of the effects mentioned above affects you severely, **tell the doctor.**

Very rare side effects (effects that occur in less than one user in 10,000):
- Swelling of the back part of the eye which may be associated with an increase in pressure inside the head and vision disturbances.

If this affects you severely, **tell the doctor**.

Side effects of unknown frequency (can not be estimated from the available data):
- Serious liver problems both, with and without yellowing of the eyes or skin, nausea, loss of appetite, dark-colored urine, swelling of the face, feet, hands and/or the whole body.
- Subcutaneous bleeding or purple skin patches, sudden bleeding for no apparent reason.
- Migraine or severe headache, often with nausea and vomiting and photosensitivity.
- Pain in the legs and feet.

If any of the effects mentioned above affects you severely, **tell the doctor**.

Additional side effects in children and adolescents
There are no additional side effects expected in children and adolescents as compared to adults.

If a side effects 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.

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 at a temperature below 30°C.
- After opening the ampoule, dilute its content immediately.
- Discard the diluted solution after 24 hours.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Castor oil, polyoxyethylated (35); Ethanol 94% w/w

What the medicine looks like and the contents of the package:
The package contains 10 transparent, glass ampoules containing 5 ml of clear yellowish-brown, oily concentrate.
The medicine is intended for use by your doctor or nurse for preparation of a solution, that will be given to you by slow infusion into the vein.

Registration Holder and Importer and its address: Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

Revised in July 2022 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 042 39 22691

Instructions for healthcare professionals on how to prepare and administer the preparation.

The concentrate should be diluted 1:20 to 1:100 with normal saline or 5% glucose and given as a slow intravenous infusion over approximately 2 to 6 hours.
Once an ampoule is opened, the contents should be used immediately. Diluted infusion solutions must be discarded after 24 hours.

Incompatibilities
Sandimmun concentrate for infusion contains macrogolglycerol ricinoleate (Castor oil, polyethoxylated), which can cause phathalate stripping from polyvinyl chloride. If available, glass containers should be used for infusion. Plastic bottles should be used only if they conform to the requirements for "Sterile plastic containers for human blood and blood components" or "Empty sterile containers of plasticised polyvinyl chloride for human blood and blood components" of the current European Pharmacopoeia. Containers and stoppers should be free of silicone oil and fatty substances.