

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNEORAL®

cyclosporine capsules for microemulsion, cyclosporine oral solution for microemulsion

PrSANDIMMUNE® I.V.

cyclosporine for injection

Read this carefully before you start taking **NEORAL® or SANDIMMUNE® I.V.** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NEORAL or SANDIMMUNE I.V.**.

Serious Warnings and Precautions

- **Transplant Patients:**
 - You will be prescribed NEORAL or SANDIMMUNE I.V. by a healthcare professional experienced in using immunosuppressive drugs and in the management of organ transplant patients.
 - Your healthcare professional will be in direct contact with your transplant centre.
 - You must be treated in a medical centre with experienced healthcare professionals where your blood levels of cyclosporine can be monitored.
- **Patients with Psoriasis, Rheumatoid Arthritis and Nephrotic Syndrome:**
 - You will be prescribed NEORAL by a healthcare professional experienced with its use. They will closely monitor you while you are being treated.
 - If you are taking NEORAL to treat your psoriasis and you have previously been treated with PUVA, methotrexate, other immunosuppressive drugs, UVB, coal tar or radiation therapy you are at an increased risk of developing skin cancer.

What is NEORAL and SANDIMMUNE I.V. used for?

NEORAL and SANDIMMUNE I.V. are indicated for the treatment of:

- Organ Transplant: Used to prevent rejection after an organ transplant. It is also used to treat organ rejection in patients who have been treated with other immunosuppressive drugs.

- Bone Marrow Transplant: Used to prevent rejection after a bone marrow transplant. It is also used to prevent or treat graft-versus-host-disease (GVHD).

NEORAL is also indicated for the treatment of:

- Psoriasis: Used to treat severe psoriasis in patients who can't use the usual treatments or in patients who did not respond to the usual treatments.
- Rheumatoid Arthritis: Used to treat severe rheumatoid arthritis in patients who can't use the usual treatments or in patients who did not respond to the usual treatments.
- Nephrotic Syndrome: Used to treat kidney problems that are also being treated with steroids or are resistant to treatment with steroids.

How does NEORAL and SANDIMMUNE I.V. work?

NEORAL and SANDIMMUNE I.V. contain the medicinal ingredient cyclosporine. It belongs to a class of drugs called immunosuppressants. These drugs work to suppress or reduce your body's immune response. Normally your body's immune system works to protect you from infections and other foreign material. When you receive a transplant, this system does not recognize the new organ, and will try to reject it. NEORAL and SANDIMMUNE I.V. work to reduce this response, so your body is more likely to accept the new organ.

NEORAL and SANDIMMUNE I.V. do not completely suppress the immune system, so your body will still have some infection-fighting ability.

NEORAL and SANDIMMUNE I.V. may be given alone but are often given with other drugs which also suppress your immune system. Together they help prolong the life of an organ transplant, or to suppress certain functions of your immune system to treat your psoriasis, rheumatoid arthritis or nephrotic syndrome.

What are the ingredients in NEORAL and SANDIMMUNE I.V.?

Medicinal ingredients: cyclosporine

Non-medicinal ingredients:

- NEORAL capsules: aluminum chloride, carminic acid (25 mg, 100 mg capsules), DL- α -Tocopherol, ethanol (9.4% w/v), gelatin, glycerol, hydrogenated castor oil, hydroxypropyl methylcellulose, iron oxide black (25 mg, 100 mg capsules), maize oil, propylene glycol, sodium hydroxide, titanium dioxide.
- NEORAL oral solution: DL- α -Tocopherol, ethanol (9.5% w/v), hydrogenated castor oil, maize oil, propylene glycol.
- SANDIMMUNE I.V.: castor oil, ethanol (278 mg/mL).

NEORAL and SANDIMMUNE I.V. comes in the following dosage forms:

NEORAL:

soft gelatin capsules; 10 mg, 25 mg, 50 mg, 100 mg
oral solution; 100 mg / mL

SANDIMMUNE I.V.:

solution for injection; 50 mg / mL

Do not use NEORAL and SANDIMMUNE I.V. if:

- you have ever had a bad, unusual or allergic reaction to cyclosporine or any of the non-medicinal ingredients of NEORAL or SANDIMMUNE I.V. (**See "What are the ingredients in NEORAL and SANDIMMUNE I.V.?"**)
- you are being treated for psoriasis, rheumatoid arthritis or nephrotic syndrome and you have one of the following conditions:
 - kidney problems (except for nephrotic syndrome);
 - uncontrolled blood pressure;
 - any type of cancer (except a skin cancer which is not a melanoma);
 - uncontrolled infection (not treated or cured);
 - inherited or acquired immune deficiency.
- you are taking bosentan, used to treat high blood pressure in the lungs

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NEORAL and SANDIMMUNE I.V. Talk about any health conditions or problems you may have, including:

- if any of the following apply because NEORAL and SANDIMMUNE I.V. contain alcohol:
 - you have or had alcohol related problems
 - you have epilepsy
 - you have any liver problems
 - you are pregnant
 - you are breastfeeding
 - the medicine is to be given to a child
- if you are to receive any vaccinations. NEORAL and SANDIMMUNE I.V. may make vaccinations less effective or increase your risk of getting an illness from a live vaccine.
- if you have high levels of potassium in your blood.
- if you suffer from gout.

Other warnings you should know about:

Tell all healthcare professionals you see (doctors, dentists, nurses, pharmacists) that you are taking NEORAL or SANDIMMUNE I.V. It is also a good idea to wear a Medic-Alert bracelet.

Immune system effects:

- NEORAL and SANDIMMUNE I.V. suppress the function of your immune system. This means you are more likely to get bacterial, fungal or viral infections. To help reduce complications from these infections, talk to your healthcare professional immediately if you get any cold or flu-like symptoms (such as a fever or sore throat), any boils on your skin, or have pain when you urinate.
- The suppressed function of your immune system may also increase your chances of developing cancer. Although very rare, cancers of the white blood cells (lymphomas) and other types of cancer have occurred in people taking cyclosporine. To help detect any cancers as soon as possible, talk to your healthcare professional immediately if you have any of these symptoms:
 - a change in your bowel or bladder habits
 - any sore that doesn't heal
 - unusual bleeding or discharge
 - the appearance of a lump or thickened area in your breast or anywhere else on your body
 - unexplained stomach upset or any trouble with swallowing
 - an obvious change in a wart or a mole
 - a nagging cough or hoarseness
 - night sweats

Progressive multifocal leukoencephalopathy: Treatment with NEORAL or SANDIMMUNE I.V. can cause a serious infection of the brain called progressive multifocal leukoencephalopathy (PML). Talk to your healthcare professional immediately if you experience vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say and muscle weakness, as these can be signs of PML.

Pregnancy and Breastfeeding:

- Do not take NEORAL or SANDIMMUNE I.V. if you are pregnant.
- You must use a reliable method of birth control while you are being treated with NEORAL and SANDIMMUNE I.V. and for 2 months after stopping treatment.
- Talk to your healthcare professional immediately if you become pregnant, or think you might be pregnant, while you are taking NEORAL or SANDIMMUNE I.V. You will want to discuss the possible benefits and risks of continuing with this drug.
- Do not breastfeed while you are taking NEORAL or SANDIMMUNE I.V. as it passes into breast milk and may harm your baby. Talk to your healthcare professional about other ways to feed your baby.

Blood tests and monitoring: Be sure to keep all appointments at your clinic. Some of these visits will be used to check the level of cyclosporine in your blood. For transplant patients, levels that are too low can cause transplant rejection, while levels that are too high may cause damage to other organs. It is therefore very important not to miss any tests or check-ups with

your healthcare professional. Your liver and kidney function and your blood lipids (cholesterol) should be checked regularly. Your healthcare professional will also check your blood pressure before you start treatment and regularly thereafter.

Driving and using machines:

You may feel sleepy, disoriented, or have blurred vision, or experience seizures (fits), coordination or movement problems, or altered thinking or behavior after taking NEORAL. Be careful when driving or operating machinery while you are taking NEORAL until you know how it affects you.

Use in the elderly (65 years of age and older): There is limited experience with the use of NEORAL or SANDIMMUNE I.V. in the elderly. Your healthcare professional will closely monitor your kidney function. If you are over the age of 65 years with psoriasis, you should only be treated in case of disabling disease.

Transplant patients: Your healthcare professional may give you magnesium supplements since NEORAL and SANDIMMUNE I.V. may reduce the amount of magnesium in your body.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NEORAL and SANDIMMUNE I.V.:

- medicines that may affect your blood potassium levels, such as potassium containing medicines or potassium sparing medicines (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists)
- certain blood pressure lowering medicines called calcium antagonists
- methotrexate, a medicine used to treat cancer, severe psoriasis and severe rheumatoid arthritis
- medicines which may increase or decrease the blood levels of NEORAL or SANDIMMUNE I.V.:
 - medicines which may decrease NEORAL or SANDIMMUNE IV blood levels: barbiturates (medicines used to help you sleep), certain anticonvulsives, used to prevent seizures (e.g. carbamazepine, phenytoin, oxcarbazepine), octreotide, an antibiotic medicine used to treat tuberculosis, orlistat (used to help weight loss), herbal medicines containing St. John's Wort (used to treat depression), ticlopidine (used after stroke), certain blood pressure lowering medicines (bosentan), and an antifungal medicine used to treat infections of the toes and nails (terbinafine).
 - medicines which may increase NEORAL or SANDIMMUNE IV blood levels: antibiotics of the macrolides type (e.g. erythromycin, azithromycin), antifungal medicine of the azole type (e.g. voriconazole, itraconazole), medicines used for heart problems or high blood

pressure (e.g. diltiazem, nicardipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral birth control, danazol (used to treat menstrual disorders), medicines used to treat gout (e.g. allopurinol, colchicines), cholic acid and derivatives (used to treat gallstones), protease inhibitors used to treat HIV, imatinib (used to treat leukemia or tumors), nefazodone (used to treat depression).

- other medicines which may affect the kidneys, such as antibiotic medicines (e.g. gentamycin, tobramycin, ciprofloxacin), antifungal medicines containing amphotericin B, antibiotic medicines containing ciprofloxacin, medicines used to treat urinary tract infection containing trimethoprim, anti-cancer agents containing melphalan, medicines used to reduce the amount of acid in your stomach (acid secretion inhibitors of the H₂-receptor antagonist type), other immunosuppressive drugs called calcineurin inhibitors (e.g. tacrolimus), pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibrin acid derivatives (e.g. bezafibrate, fenofibrate) used to lower fat in the blood.
- nifedipine (used to treat high blood pressure and heart pain).
- medicines whose concentrations may increase when used together with NEORAL including lercanidipine (used to lower high blood pressure), aliskiren (used to treat high blood pressure), digoxin (used to treat heart problems), cholesterol lowering agents (HMG-CoA reductase inhibitors, also called statins), prednisolone (a steroid medicine used to treat inflammation), etoposide (used to treat cancer), dabigatran (oral blood thinner used to prevent stroke), repaglinide (oral medicine to treat diabetes), immunosuppressives (e.g. everolimus, sirolimus), ambrisentan and specific anticancer medicines called anthracyclines (e.g. doxorubicin).
- medicines whose concentration may decrease when used together with NEORAL or SANDIMMUNE I.V. including mycophenolate sodium or mofetil (an immunosuppressant) and eltrombopag (used to treat bleeding disorders).
- caspofungin, used to treat fungal infections.

Do not take NEORAL or SANDIMMUNE I.V. with grapefruit juice.

How to take NEORAL and SANDIMMUNE I.V.?

- Always take NEORAL or SANDIMMUNE I.V. exactly as your healthcare professional has told you. You should check with your healthcare professional if you are unsure.
- NEORAL is an oral medicine that you will take in either capsule or liquid form.
- SANDIMMUNE I.V. is an intravenous medicine that will be given to you by your healthcare professional directly into your vein, usually while you are in the hospital.
- **Do not stop taking NEORAL or SANDIMMUNE I.V. on your own even if you have been taking it for several years. Transplant patients:** Although you may not notice any symptoms of rejection for several weeks, missing even a few doses of NEORAL or SANDIMMUNE I.V. may lead to rejection of your transplanted organ.
- Do not change the dose on your own, no matter how you are feeling. Blood tests are one of

the ways your healthcare professional knows how much NEORAL or SANDIMMUNE I.V. you need. Based on these tests, and on your response to this drug, your healthcare professional may change your dose from time to time.

- Space your doses of NEORAL as evenly as you can throughout the day. For example, if you take the drug 2 times a day, leave about 12 hours between each dose.
- Try to take your dose(s) at the same time(s) each day. This will help keep a constant amount of drug in your body and will also help you remember each dose. NEORAL may be taken with or without food. But it is best to be consistent: once you decide when you are going to take it in relation to food, do it the same way each time.
- Never take NEORAL or SANDIMMUNE I.V with grapefruit juice.
- Leave the NEORAL capsules in the blister foil until you need a dose. When you are ready to take a dose, remove the number of capsules you need to make up the dose your healthcare professional prescribed. NEORAL capsules have a characteristic smell when the blister foil is opened. This is normal.
- Swallow the NEORAL capsules whole. You may use any kind of drink except grapefruit juice.
- If you suffer from diarrhea or vomiting talk to your healthcare professional as this can stop your body from absorbing the right amount of NEORAL.
- If you were previously taking a different oral formulation of cyclosporine, your healthcare professional will monitor you more closely for a short period after you switch from one oral formulation to another. They will make sure that your cyclosporine blood levels are in the correct range. Never adjust the dose yourself unless your healthcare professional has told you to.

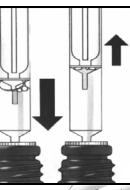
Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your body weight and the condition that is being treated. If you are a transplant patient they will also use your blood levels of cyclosporine.

NEORAL Oral Solution

To open the bottle for the first time:

1.	Raise the plastic cap.	
2.	Tear off the sealing ring completely.	

3.	Remove the grey stopper and throw it away.	
4.	Push the tube unit with the white stopper firmly into the neck of the bottle.	
5.	Insert the nozzle of the syringe into the white stopper.	
6.	Draw up prescribed volume of solution (position the lower part of the plunger ring in front of the graduation corresponding to the prescribed volume).	
7.	Expel any large bubbles by depressing and withdrawing plunger a few times before removing syringe containing prescribed dose from bottle. The presence of a few tiny bubbles is of no importance and will not affect the dose in any way.	
8.	Push the medicine out of the syringe into a small glass with some liquid, but no grapefruit juice. <u>Do not let the syringe touch the liquid in the cup. Most drinks other than grapefruit juice can be used at room temperature, for example, apple juice, orange juice, or a soft drink. Once you have chosen a drink, use the same one each time.</u> The medicine can be mixed just before you take it. Stir and drink the entire mixture right away. Please take the medicine immediately after preparation.	
9.	After use, wipe syringe on outside only with a dry tissue and replace in its case. Do not rinse the syringe with water, alcohol, or any other liquid. White stopper and tube should remain in bottle. Close bottle with cap provided.	

Once the bottle is opened the first time, you can start at point number 5 above for your next dose.

- Each dose of NEORAL oral solution must be measured accurately. Be sure to ask your healthcare professional if you have any question about how to measure the solution.

Overdose:

If you think you, or a person you are caring for, have taken too much NEORAL or SANDIMMUNE I.V., contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember, unless it is almost time for your next dose. Then skip the missed dose and go on as before. It is a good idea to ask your healthcare professional ahead of time what to do about missed doses.

- For transplant patients, missing even a few doses of NEORAL or SANDIMMUNE I.V. may lead to rejection of your transplanted organ. That is why it is so important to take each of the doses your healthcare professional prescribes.
- Talk to your healthcare professional if you have trouble remembering doses, or if you are uncertain about how to take them. Also be sure to discuss any concerns you have about taking this drug as prescribed. Your healthcare professional can often suggest ways to overcome problems you have taking your medication.
- Never allow your medication to run out between refills. Plan to order your refills about one week ahead of time — that way you will always have a supply in case the pharmacy is closed or out of the drug. Also be sure to take enough medication with you when you go on a holiday.

What are possible side effects from using NEORAL and SANDIMMUNE I.V.?

These are not all the possible side effects you may have when taking NEORAL or SANDIMMUNE I.V. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache (including migraine with vomiting and sensitivity to light)
- loss of appetite, nausea, vomiting, constipation or diarrhea
- weight gain
- acne or oily skin
- slight trembling of the hands
- increased growth of fine hairs on the body
- muscle or joint pains or cramping
- muscle spasm
- pain in legs and feet
- weakness, anxiety
- tingling in the fingers, toes or mouth
- night sweats

- hearing loss
- tender or swollen gums
- hot flushes
- rash
- breast enlargement in men

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
High blood pressure: headache, chest pains, vision problems, ringing in the ears			✓
Kidney problems: decreased urination, nausea, vomiting, swelling of the extremities, fatigue			✓
High blood sugar: frequent urination, thirst, hunger		✓	
COMMON			
Low levels of white blood cells: bacterial, fungal or viral infections, fatigue, fever, sore throat, aches and pains, flu-like symptoms, boils on your skin, pain when urinating			✓
Ulcers: stomach pain during or after eating, burning or dull pain, feeling full, bloating		✓	
Convulsions: seizure or fits, with or without loss of consciousness			✓
UNCOMMON			
Low levels of red blood cells or platelets: pale skin, tiredness, breathlessness, dark urine (sign of breakdown of red blood cells), bruising or bleeding with no obvious reasons, confusion, disorientation, decreased alertness, kidney problems			✓
Liver problems: yellowing of the skin and/or eyes, dark urine, pale stool, abdominal pain, vomiting and nausea, loss of appetite			✓
Allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
RARE			
Abnormal menstrual cycle		✓	
Inflammation of the pancreas: severe abdominal pain that lasts and gets worse when you lie down, nausea, vomiting			✓
VERY RARE			

Cancer: a change in your bowel or bladder habits, any sore that doesn't heal, unusual bleeding or discharge, the appearance of a lump or thickened area in your breast or anywhere else on your body, unexplained stomach upset or any trouble with swallowing, an obvious change in a wart or a mole, a nagging cough or hoarseness, night sweats		✓	
UNKNOWN FREQUENCY			
Benign intracranial hypertension (increased pressure in the head): swelling at the back of the eyes which may be associated with blurred vision and possible visual impairment			✓
High levels of potassium in the blood: irregular heartbeat, muscle weakness, generally feeling unwell			✓
Low levels of magnesium in the blood: loss of appetite, nausea and vomiting, fatigue, weakness, shaking, pins and needles, muscle spasms		✓	
Brain disorders: seizures, confusion, disorientation, decreased responsiveness, personality changes, agitation, sleeplessness, sight disturbances, blindness, coma, paralysis of part or all of the body, stiff neck, loss of coordination with or without abnormal speech and eye movements			✓
High levels of uric acid in the blood: severe joint pain, joint stiffness, redness and swelling		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

**NEORAL® (Cyclosporine) capsules, oral solution for microemulsion
SANDIMMUNE® (Cyclosporine) concentrate for solution for infusion**

Keep NEORAL and SANDIMMUNE I.V. out of reach and sight of children.

- A child who accidentally takes this drug may be seriously harmed. A locked drawer or cupboard is best if you have small children in the house.
- NEORAL capsules should be kept in a dry place, at a temperature between 15 and 25°C. Remember to leave each capsule in its foil pack until you need to take it.
- NEORAL oral solution should be kept at room temperature (15-30°C), preferably not below 20°C for prolonged periods. Do not put it in the fridge, and do not let it freeze. Once the bottle has been opened, the contents must be used within 2 months. Be sure to keep the solution in the original bottle.
- A jelly-like formation may occur if the oral solution goes below 20°C. This should go away when the solution is warmed to 30°C. Little flakes (or a slight sediment) may still be seen. Having this happen does not change the effectiveness or safety of the product, and dosing by means of the syringe remains accurate.

If you want more information about NEORAL and SANDIMMUNE I.V.:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: February 23, 2023

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