

PART III: CONSUMER INFORMATION

PrNEORAL[®]
(cyclosporine capsules)
(cyclosporine oral solution)
for microemulsion

AND

PrSANDIMMUNE[®] I.V.
(cyclosporine for injection)

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

Read this information carefully, even if you have already been taking NEORAL[®] or SANDIMMUNE[®] I.V.

This information should not replace your doctor's or pharmacist's advice. If any information in this text concerns you, talk to your doctor or pharmacist right away.

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed the drug NEORAL[®] or SANDIMMUNE[®] I.V.. It is used after organ or bone marrow transplantations to help prevent organ rejection, or to treat autoimmune conditions such as severe psoriasis, severe rheumatoid arthritis and nephrotic syndrome.

NEORAL[®] or SANDIMMUNE[®] I.V. are the brand name for a drug called "cyclosporine". It belongs to a family of drugs known as "immunosuppressants". These drugs work to "suppress" or reduce the body's immune response.

What it does:

Your body's immune system normally 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 these help prolong the life of an organ transplant, or to suppress certain function of your immune system to treat your psoriasis, rheumatoid arthritis or nephrotic syndrome.

When it should not be used:

Do not use NEORAL[®] or 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 the important non-medicinal ingredients are"**)

For the treatment of psoriasis, rheumatoid arthritis and nephrotic syndrome, do not take NEORAL[®] or SANDIMMUNE[®] I.V. if you have one of the following conditions:

- abnormal kidney function (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.

Do not use NEORAL[®] or SANDIMMUNE[®] I.V. with bosentan.

What the medicinal ingredient is:

NEORAL[®] contains cyclosporine for microemulsion.

NEORAL[®] is the microemulsion formulation of cyclosporine which can be taken orally, while SANDIMMUNE[®] is the intravenous form of cyclosporine which you may need to receive during your stay in hospital.

The "microemulsion" formulation allows more reliable absorption of cyclosporine from your stomach compared to conventional types of oral dosage forms. This means almost the same amount will go into your body each time you take the drug, and that food will have less of an effect on the amount of cyclosporine that gets absorbed.

SANDIMMUNE[®] I.V. contains cyclosporine for injection.

What the important non-medicinal ingredients are:

Non-medicinal ingredients for NEORAL[®] capsules are the following: DL- α -Tocopherol, ethanol, propylene glycol, maize oil, hydrogenated castor oil. Capsule shell: glycerol, propylene glycol, gelatin, iron oxide black, titanium dioxide. Imprint: caminic acid, aluminum chloride, sodium hydroxide, hydroxypropyl methylcellulose.

Non-medicinal ingredients for NEORAL[®] oral solution are the following: DL- α -Tocopherol propylene glycol, ethanol, maize oil, hydrogenated castor oil.

Non-medicinal ingredients for SANDIMMUNE® I.V. are the following: ethanol and castor oil.

What dosage forms it comes in:

NEORAL® comes in two forms: a soft gelatin **capsule** and an **oral solution**. The following points tell you how to take the form you have been given.

Capsules

NEORAL® capsules come with 10 mg, 25 mg, 50 mg or 100 mg of cyclosporine. Each capsule is contained in a foil strip.

Solution

NEORAL® solution comes in 50 millilitre bottles.

SANDIMMUNE® I.V. (concentrate for solution for infusion), is supplied in 1 mL and 5 mL sterile ampoules containing 50 mg of cyclosporine per mL in a polyoxyethylated castor oil and ethanol.

WARNINGS AND PRECAUTIONS

Medicines which suppress the immune system, such as NEORAL® or SANDIMMUNE® I.V. may influence your body's ability to fight against infection and may increase the risk of developing cancers, particularly of the skin and lymphoid system. Therefore you should limit your exposure to sunlight and UV light by wearing appropriate protective clothing and frequently applying a sunscreen with a high protection factor.

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

Before you use and because of the alcohol contained in NEORAL® or SANDIMMUNE® I.V., talk to your doctor or pharmacist if:

- You have or had alcohol related problems
- You have epilepsy or have any liver problems
- You are pregnant
- You breast-feed your child
- The medicine is given to a child

Before you use NEORAL® or SANDIMMUNE® I.V. talk to your doctor or pharmacist if:

- You have any current or have had past health conditions.
- **You are taking other drugs:** Do not take any other drugs without asking your doctor or pharmacist first including over-the-counter medicines and herbal or home remedies. NEORAL® or SANDIMMUNE® I.V. is often given with other medicines. Make sure you know if you are to stop, or to continue, other immunosuppressant drugs you had been taking.

- **You are to receive vaccinations:** NEORAL® or

SANDIMMUNE® I.V. may make vaccinations less effective or increase your risk of getting an illness from a live vaccine. Always discuss this possibility with your doctor before you get any vaccinations or immunizations.

- **You receive NEORAL® or SANDIMMUNE® I.V.** the level of cyclosporine in your blood (especially for transplant patients), your liver and kidney function and your blood lipids should be checked regularly. Your blood pressure should be checked before initiation of therapy and regularly thereafter. If high blood pressure develops during therapy and cannot be controlled, treatment should be stopped.

- **You have high levels of potassium in your blood.**

- **You suffer from gout.**

- **You have had a transplant or just after your operation,** your doctor may give you magnesium supplements due to the fact that NEORAL® or SANDIMMUNE® I.V. may reduce the amount of magnesium in your body.

- **You are or become pregnant:** There is an increased risk of difficult pregnancies (up to 25% of pregnancies) in patients who have taken cyclosporine during pregnancy. These difficult pregnancies have resulted in an increased risk to the babies during and immediately after birth. As well, some babies have been born with abnormalities.

For these reasons it is recommended that you do not take NEORAL® or SANDIMMUNE® I.V. if you are, or become, pregnant. During your treatment with NEORAL® and for 2 months after stopping your NEORAL® or SANDIMMUNE® I.V. treatment, you must use a reliable method of birth control. Should you become pregnant during the time you are taking your NEORAL® or SANDIMMUNE® I.V. you should inform your doctor at once. You will want to discuss the possible benefits and risks of continuing with this drug.

- **You are breast-feeding:** Do not breast feed your baby if you are taking NEORAL® or SANDIMMUNE® I.V. as it passes into breast milk and may harm your baby.

There is a limited experience with NEORAL® or SANDIMMUNE® I.V. in elderly. Your renal function should be monitored with particular care. If you are over the age of 65 years with psoriasis, you should only be treated in case of disabling disease.

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.

INTERACTIONS WITH THIS MEDICATION

Make sure your doctor knows if you are taking, or begin to take, any other medicines, including drugs, or herbal (natural) products that you can buy without a prescription while you take NEORAL® or SANDIMMUNE® I.V.. Some medicines may interact with NEORAL® or SANDIMMUNE® I.V. such as:

- medicines that may impact your 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 reducing agents of the calcium antagonist type
- methotrexate, a medicine to treat tumors, severe psoriasis and severe rheumatoid arthritis
- medicines which may increase or reduce the blood levels of NEORAL® or SANDIMMUNE® I.V. The doctor might check the cyclosporine concentration in your blood when initiating or discontinuing other medical treatment.
 - medicines which may decrease the NEORAL® concentrations: barbiturates (medicines used to help to sleep), certain anticonvulsives (e.g. carbamazepine, phenytoin), octreotide, antibacterial medicines used to treat tuberculosis, orlistat (used to help weight loss), herbal medicines containing St. John's Wort, ticlopidine (used after stroke), certain blood pressure reducing agents (bosentan), and an antifungal medicine used to treat infections of the toes and nails (terbinafine).
 - medicines which may increase NEORAL® concentrations: antibiotics of the macrolides type (e.g. erythromycin, azithromycin), antifungal medicine of the azole type (voriconazole, itraconazole), medicines used for heart problems or high blood pressure (diltiazem, nifedipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral contraceptives, danazol (used to treat menstrual disorders), medicines used to treat gout (allopurinol), cholic acid and derivatives (used to treat gallstones), protease inhibitors used to treat HIV, imatinib (used to treat leukaemia or tumors), colchicines
 - other medicines which may affect the kidneys, such as antibacterial agents (gentamycin, tobramycin, ciprofloxacin), antifungal agents containing amphotericin B, antibacterial agents containing ciprofloxacin, agents against urinary tract infection containing trimetoprim, 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), tacrolimus, pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibric acid derivatives (e.g. bezafibrate, fenofibrate) used to lower fat in the blood.
 - nifedipine (used to treat high blood pressure and heart pain), you might get swollen gums that spread over your teeth.
 - medicines whose concentrations may increase when used together with NEORAL® including aliskiren (to treat

high blood pressure), digoxin (used to treat heart problems), cholesterol lowering agents (HMG-CoA reductase inhibitors (also called statins), prednisolone, etoposide (used to treat cancer), dabigatran (oral anticoagulant used to prevent stroke), repaglinide (oral antidiabetic agent), immunosuppressives (everolimus, sirolimus), ambrisentan and specific anticancer medicines called anthracyclines (e.g. doxorubicine).

- caspofungin
- lercanidipine
- oxcarbazepine
- nefazodone

Never take NEORAL® or SANDIMMUNE® I.V. with grapefruit juice.

NEORAL® or SANDIMMUNE® I.V. is also used in combination with other immunosuppressive agents. However, do not use it together with other calcineurin inhibitors such as tacrolimus.

Use of NEORAL® or SANDIMMUNE® I.V. with aliskiren is not recommended and use of NEORAL® or SANDIMMUNE® I.V. with dabigatran should be avoided.

PROPER USE OF THIS MEDICATION

Usual dose:

- Always take NEORAL® or SANDIMMUNE® I.V. exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. Do not change the dose on your own, no matter how you are feeling. Blood tests are one of the ways your doctor tells how much NEORAL® or SANDIMMUNE® I.V. you need. Based on these tests, and on your response to this drug, your doctor 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 capsules in the 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 doctor prescribed.

- Swallow the capsules whole. You may use any kind of drink except grapefruit juice.

- If you were previously taking a different oral formulation of cyclosporine, your doctor will monitor you more closely for a short period following transfer from one oral formulation to another to ensure that cyclosporine blood levels are in the correct range. Never adjust the dose yourself unless the doctor has told you to.





SANDIMMUNE® I.V.: The usual dose is 3 to 5 mg/kg body weight per day starting on the day before your transplant and continuing for up to two weeks after the operation. You will be started on NEORAL® (capsules or oral solution) as soon as possible after the operation.


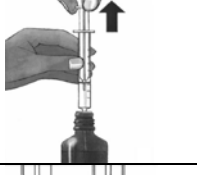
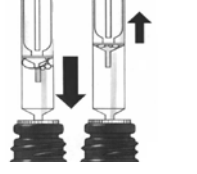


NEORAL®: If you have had an organ or bone marrow transplant, the total dose is usually within the range of 2 mg/kg body weight per day and 15 mg/kg body weight per day divided in two doses.

- For the treatment of **nephrotic syndrome**, the total daily dose is usually within the range of 2.5 mg/kg body weight per day and 5 mg/kg body weight per day.
- For the treatment of **severe rheumatoid arthritis**, the total daily dose is usually within the range of 3 mg/kg body weight per day and 5 mg/kg body weight per day divided in two doses.
- For the treatment of **psoriasis and eczema**, the total dose is usually within the range of 2.5 mg/kg body weight per day and 5.0 mg/kg body weight per day divided in two doses.
- SANDIMMUNE® I.V. will be diluted with normal saline or 5% glucose and given to you by slow infusion.

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.</u> <u>Most drinks other than grapefruit juice can be used at room temperature, for example, apple juice, orange juice, or a soft drink.</u> <u>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® solution must be measured accurately. Be sure to ask your doctor, nurse or pharmacist if you have any question about how to measure the solution.

Overdose:

In case of drug overdose, contact a health care practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

- 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 doctor prescribes.

- Talk to your doctor, nurse or pharmacist 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. These people 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.

If you forget to take a dose, take another one as soon as you remember, unless it is almost time for your next dose. Then go on as before. It is also a good idea to ask your doctor ahead of time what to do about missed doses.

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 your doctor orders.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NEORAL® or SANDIMMUNE® I.V. can cause side effects, although not everybody gets them. Be sure to talk to your doctor if you have any concerns about this.

The most common side effects noted were:

- high blood pressure;
- kidney or liver problems;
- headache (including migraine);
- increased levels of lipids (e.g. cholesterol) in the blood;
- loss of appetite, nausea, vomiting, constipation or diarrhea;
- acne or oily skin;
- slight trembling of the hands;
- increased growth of fine hairs on the body;
- muscle or joint pains or cramping;
- weakness, anxiety;
- tingling in the fingers, toes or mouth;
- night sweats; hearing loss; swelling of the face;
- increased potassium in the body (your doctor may instruct you to avoid high dietary potassium intake);
- tender or swollen gums
- decreased ability to fight infection
- low level of white blood cells
- high level of sugar in the blood
- hot flushes
- stomach ulcer
- rash
- If you develop liver problems while taking this drug, which

could occur with or without the following symptoms: jaundice (yellowing of the skin and/or eyes and/or dark urine), abdominal pain, vomiting and nausea, contact your doctor immediately.

- Because NEORAL® or SANDIMMUNE® I.V. reduces the function of your immune system, you are more likely to get bacterial, fungal or viral infections. To help reduce complications from these infections, tell your doctor right away about any cold or flu-like symptoms (such as a fever or sore throat), any boils on your skin, or pain when you urinate (pass your water).
- The decreased 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. The following are some possible warning signs of cancer. To help detect any cancers as soon as possible, report any of these symptoms to your doctor right away: 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 areas 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
- If you experience vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say, and muscle weakness, these can be the signs and symptoms of an infection of the brain called progressive multifocal leukoencephalopathy. Contact your doctor right away if these symptoms occur.
- Vomiting or diarrhea may stop NEORAL® from being absorbed (going) into your body.

Some side effects occurred with unknown frequency and were:

- Low levels of magnesium in the blood
- Vomiting and sensitivity to light
- Inflammation of the pancreas with severe upper stomach pain
- Muscle spasm
- Pain in legs and feet
- Breast enlargement in men
- Tiredness and weight gain
- High level of acid uric in the blood

Be sure to tell your doctor right away if you notice any of these symptoms listed above, and especially if they continue, bother you in any way, or seem to increase in intensity. Remember, only a doctor can tell if these symptoms might be from NEORAL® or SANDIMMUNE® I.V.. If you think you are having side effects, talk to your doctor right away. Do not stop taking this drug on your own.

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	Tremor		√	†
	High blood pressure		√	
	Tingling		√	
	Bacterial, fungal or viral infection		√	
	Vomiting or diarrhea		√	
	Muscle or joint pains or cramping		√	
	Weakness		√	
	Anxiety		√	
	Swelling at the back of the eyes which may be associated with blurred vision and possible visual impairment due to an increase in pressure inside the head (benign intracranial hypertension)		√	
	High level of potassium in the blood		√	

	Low level of red blood cells or platelets; which may be associated with pale skin, tiredness, breathlessness, dark urine (sign of breakdown of red blood cells), bruising or bleed with no obvious reasons, confusion, disorientation, decreased alertness, and kidney problems		√	
Uncommon	Ulcers		√	†
	Convulsions		√	
	Brain disorder with signs such as 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		√	
	Allergic reactions		√	
Rare	Abnormal menstrual cycle		√	
Very rare	Tumours/ malignancies		√	†

† Do not stop your medicines unless you have discussed this with your doctor first.

This is not a complete list of side effects. For any unexpected effects while taking NEORAL® or SANDIMMUNE® I.V.,

contact your doctor or pharmacist.

HOW TO STORE IT

- Keep NEORAL[®] out of the 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.

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
Post Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse 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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.novartis.ca>, or by contacting Novartis at 1-800-363-8883.

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