Package leaflet: Information for the user

[PRODUCT NAME] 200 mg powder for solution for infusion
voriconazole

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [PRODUCT NAME] is and what it is used for

[PRODUCT NAME] contains the active substance voriconazole. [PRODUCT NAME] is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:
- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp*.),
- candidaemia (another type of fungal infection due to *Candida sp.*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp*. infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp*. or *Fusarium sp*. (two different species of fungi).

[PRODUCT NAME] is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be used under the supervision of a doctor.

2. What you need to know before you use [PRODUCT NAME]

Do not use [PRODUCT NAME]:
- if you are allergic to voriconazole or any of the other ingredients of this medicine (listed in section 6).

The medicines in the following list must not be taken during your course of [PRODUCT NAME] treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heartbeat)
- Rifampicin (used for treating tuberculosis)
- Efavirenz (used for treating HIV) in doses of 400 mg and above once daily
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Ritonavir (used for treating HIV) in doses of 400 mg and more twice daily
- St. John's Wort (herbal supplement)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using [PRODUCT NAME] if:

- you have had an allergic reaction to other azoles;
- you are suffering from or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of [PRODUCT NAME]. Your doctor should also monitor your liver function while you are being treated with [PRODUCT NAME] by doing blood tests;
- you are known to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with [PRODUCT NAME]:

- tell your doctor immediately if you develop
    - sunburn
    - severe skin rash or blisters
    - bone pain

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of [PRODUCT NAME].

If you develop signs of 'adrenal insufficiency' where the adrenal glands do not produce adequate amounts of certain steroid hormones such as cortisol which may lead to symptoms such as: chronic, or long lasting fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain, please tell your doctor.

Your doctor should monitor the function of your liver and kidney by doing blood tests.

Children and adolescents
[PRODUCT NAME] must not be given to children younger than 2 years of age.

Other medicines and [PRODUCT NAME]

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Some medicines, when taken at the same time as [PRODUCT NAME], may affect the way [PRODUCT NAME] works or [PRODUCT NAME] may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with [PRODUCT NAME] at the same time should be avoided, if possible:
- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with [PRODUCT NAME] at the same time should be avoided, if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin your blood counts and side effects to rifabutin will need to be monitored.
- Phenytoin (used to treat epilepsy). If you are already being treated with phenytoin your blood concentration of phenytoin will need to be monitored during your treatment with [PRODUCT NAME] and your dose may be adjusted.

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or [PRODUCT NAME] are still having the desired effect:
- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulfonylureas (e.g. tolbutamide, glipizide and glyburide) (used for diabetes)
- Statins (e.g. atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g. midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you use [PRODUCT NAME] whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g. vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz **cannot** be taken at the same time as [PRODUCT NAME])
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)
- Tolvaptan (used to treat hyponatremia (low levels of sodium in your blood) or to slow kidney function decline in patients with polycystic kidney disease)
- Letermovir (used for preventing cytomegalovirus (CMV) disease after bone marrow transplant)
- Naloxegol: used to treat constipation specifically caused by pain medicines, called opioids, (e.g., morphine, oxycodone, fentanyl, tramadol, codeine)
- Ivacaftor: used to treat cystic fibrosis

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

[PRODUCT NAME] must not be used during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of child-bearing potential. Contact your doctor immediately if you become pregnant while being treated with [PRODUCT NAME].

Driving and using machines
[PRODUCT NAME] may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Tell your doctor if you experience this.

[PRODUCT NAME] contains sodium
Talk to your doctor or pharmacist if you need 6 or more vials daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

[PRODUCT NAME] contains hydroxypropylbetadex
If you have a kidney disease, talk to your doctor before you receive this medicine.

3. How to use [PRODUCT NAME]

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will determine your dose depending on your weight and the type of infection you have.

Your doctor may change your dose depending on your condition.

The recommended dose for adults (including elderly patients) is as follows:

	Intravenous
Dose for the first 24 hours (Loading Dose)	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4 mg/kg twice a day

Depending on your response to treatment, your doctor may decrease the dose to 3 mg/kg twice daily.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents
The recommended dose for children and adolescents is as follows:

	Intravenous	
	Children aged 2 to less than 12 years and adolescents aged 12 to 14 years weighing less than 50 kg	Adolescents aged 12 to 14 years weighing 50 kg or more; and all adolescents older than 14

Dose for the first 24 hours (Loading Dose)	9 mg/kg every 12 hours for the first 24 hours	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	8 mg/kg twice a day	4 mg/kg twice a day

Depending on your response to treatment, your doctor may increase or decrease the daily dose.

[PRODUCT NAME] powder for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information).

This will be given to you by intravenous infusion (into a vein) at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

If you or your child are taking [PRODUCT NAME] for prevention of fungal infections, your doctor may stop giving [PRODUCT NAME] if you or your child develop treatment-related side effects.

If you forget to use [PRODUCT NAME]
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or pharmacist if you think that a dose has been forgotten.

If you stop using [PRODUCT NAME]
[PRODUCT NAME] treatment will continue for as long as your doctor advises, however, duration of treatment with [PRODUCT NAME] powder for solution for infusion should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning. You may be switched from the intravenous infusion to tablets once your condition improves.

When [PRODUCT NAME] treatment is stopped by your doctor, you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects - Stop taking [PRODUCT NAME] and see a doctor immediately if you experience:
- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common: may affect more than 1 in 10 people
- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, colour blindness, eye disorder, halo vision, night blindness, swinging vision, seeing sparks, visual aura, visual acuity reduced, visual brightness, loss of part of the usual field of vision, spots before the eyes)
- Fever
- Rash
- Nausea, vomiting, diarrhea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes

Common: may affect up to 1 in 10 people
- Inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Acute breathing difficulty, chest pain, swelling of the face (mouth, lips and around eyes), fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver and liver injury
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps, redness of the skin
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon: may affect up to 1 in 100 people
- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain

- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch
- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes with erratic electrical impulses
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including life-threatening skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response

Rare: may affect up to 1 in 1,000 people
- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Loss of most fibers in the optic nerve, clouding of the cornea, involuntary movement of the eye
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Heart rhythm or conduction problems (sometimes life-threatening)
- Life-threatening allergic reaction
- Disorder of blood clotting system
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life-threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below
- Small dry scaly skin patches, sometimes thick with spikes or 'horns'

Side effects with frequency not known (cannot be estimated from the available data):
- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:
- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

Reactions during the infusion have occurred uncommonly with [PRODUCT NAME] (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As [PRODUCT NAME] has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

There have been reports of skin cancer in patients treated with [PRODUCT NAME] for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.

If any of these side effects persist or are troublesome, please tell your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [PRODUCT NAME]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions before opening.

Chemical and physical in-use stability has been demonstrated for 72 hours at 25 °C and at 2 °C - 8 °C.
From a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C - 8 °C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions. Reconstituted [PRODUCT NAME] needs to be diluted with a compatible infusion solution first before it is infused. (Please refer to the end of this leaflet for further information).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [PRODUCT NAME] contains
- The active substance is voriconazole.
  Each vial contains 200 mg of voriconazole. After reconstitution, each mL of the solution contains 10 mg of voriconazole.
- The other ingredients are hydroxypropylbetadex, sodium chloride, hydrochloric acid (for pH adjustment).

What [PRODUCT NAME] looks like and contents of the pack
Each carton contains one vial. [PRODUCT NAME] is presented as a white to off-white lyophilized powder for solution for infusion in 25 mL clear glass vial type I with a grey, chlorobutyl rubber stopper and aluminium cap with plastic red flip-off seal.

Marketing Authorisation Holder
<[To be completed nationally]>

Manufacturer
<[To be completed nationally]>

This medicinal product is authorised in the Member States of the EEA under the following names:

Netherlands	Voriconazole Pharmathen 200mg poeder voor oplossing voor infusie
Spain	Voriconazol Aurovitas Spain 200 mg polvo para solución para perfusión EFG
France	Voriconazole OHRE Pharma 200 mg poudre pour solution pour perfusion
Italy	VORICONAZOLO AHCL
United Kingdom	Voriconazole 200 mg powder for solution for infusion PL 35533/0036
Germany	Voriconazol PUREN 200 mg Pulver zur Herstellung einer Infusionslösung ENR 2191998
Poland	Voriconazole Genoptim 200 mg proszek do sporzadania roztworu do infuzji
Croatia	Vorikonazol PharmaS 200 mg prašak za otopinu za infuziju

This leaflet was last revised in

The following information is intended for healthcare professionals only:

Reconstitution and Dilution information
- [PRODUCT NAME] powder for solution for infusion needs first to be reconstituted with either 19 mL of water for injections or 19 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL voriconazole.
- Discard the [PRODUCT NAME] vial if the vacuum does not pull the diluent into the vial.
- It is recommended that a standard 20 mL (non-automated) syringe be used to ensure that the exact amount (19.0 mL) of water for injections or of sodium chloride 9 mg/mL (0.9 %) solution for injection is dispensed.
- The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final [PRODUCT NAME] solution containing 0.5 to 5 mg/mL of voriconazole.
- This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.
- Not for administration as a bolus injection.
- For storage information, please refer to Section 5 ‘How to store [PRODUCT NAME]’.

Required Volumes of 10 mg/mL [PRODUCT NAME] Concentrate

Body Weight (kg)	Volume of [PRODUCT NAME] Concentrate (10 mg/mL) required for:				
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 mL (1)	-	8.0 mL (1)	9.0 mL (1)
15	-	6.0 mL (1)	-	12.0 mL (1)	13.5 mL (1)
20	-	8.0 mL (1)	-	16.0 mL (1)	18.0 mL (1)
25	-	10.0 mL (1)	-	20.0 mL (1)	22.5 mL (2)
30	9.0 mL (1)	12.0 mL (1)	18.0 mL (1)	24.0 mL (2)	27.0 mL (2)
35	10.5 mL (1)	14.0 mL (1)	21.0 mL (2)	28.0 mL (2)	31.5 mL (2)
40	12.0 mL (1)	16.0 mL (1)	24.0 mL (2)	32.0 mL (2)	36.0 mL (2)
45	13.5 mL (1)	18.0 mL (1)	27.0 mL (2)	36.0 mL (2)	40.5 mL (3)
50	15.0 mL (1)	20.0 mL (1)	30.0 mL (2)	40.0 mL (2)	45.0 mL (3)
55	16.5 mL (1)	22.0 mL (2)	33.0 mL (2)	44.0 mL (3)	49.5 mL (3)
60	18.0 mL (1)	24.0 mL (2)	36.0 mL (2)	48.0 mL (3)	54.0 mL (3)
65	19.5 mL (1)	26.0 mL (2)	39.0 mL (2)	52.0 mL (3)	58.5 mL (3)
70	21.0 mL (2)	28.0 mL (2)	42.0 mL (3)	-	-
75	22.5 mL (2)	30.0 mL (2)	45.0 mL (3)	-	-
80	24.0 mL (2)	32.0 mL (2)	48.0 mL (3)	-	-
85	25.5 mL (2)	34.0 mL (2)	51.0 mL (3)	-	-
90	27.0 mL (2)	36.0 mL (2)	54.0 mL (3)	-	-
95	28.5 mL (2)	38.0 mL (2)	57.0 mL (3)	-	-
100	30.0 mL (2)	40.0 mL (2)	60.0 mL (3)	-	-

[PRODUCT NAME] is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the reconstituted solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C - 8 °C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions. Reconstituted [PRODUCT NAME] needs to be diluted with a compatible infusion solution first before it is infused.

Compatible Infusion Solutions:
The reconstituted solution can be diluted with:

Sodium Chloride 9 mg/mL (0.9 %) Solution for Injection
Compound Sodium Lactate Intravenous Infusion
5 % Glucose and Lactated Ringer's Intravenous Infusion
5 % Glucose and 0.45 % Sodium Chloride Intravenous Infusion
5 % Glucose Intravenous Infusion
5 % Glucose in 20 mEq Potassium Chloride Intravenous Infusion
0.45 % Sodium Chloride Intravenous Infusion
5 % Glucose and Sodium Chloride 9 mg/mL (0.9 %) Solution for Injection

The compatibility of [PRODUCT NAME] with diluents other than listed above (or listed below under 'Incompatibilities') is unknown.

Incompatibilities:
[PRODUCT NAME] must not be infused into the same line or cannula concomitantly with other medicinal infusion products, including parenteral nutrition (e.g. Aminofusin 10 % Plus).

Infusions of blood products must not occur simultaneously with [PRODUCT NAME].

Infusion of total parenteral nutrition can occur simultaneously with [PRODUCT NAME] but not in the same line or cannula.

[PRODUCT NAME] must not be diluted with 4.2 % Sodium Bicarbonate Infusion.