PACKAGE LEAFLET: INFORMATION FOR THE USER

Voriconazole Rowex 200 mg Powder for Solution for Infusion

voriconazole

Read all of this leaflet carefully before you start taking 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 Voriconazole Rowex is and what it is used for

Voriconazole Rowex contains the active substance voriconazole. Voriconazole Rowex 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).

Voriconazole Rowex 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 take Voriconazole Rowex

Do not take Voriconazole Rowex:
- If you are allergic to the active ingredient voriconazole, or to sulphobutylether beta cyclodextrin sodium (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your Voriconazole Rowex 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 taking Voriconazole Rowex 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 Voriconazole Rowex. Your doctor should also monitor your liver function while you are being treated with Voriconazole Rowex by doing blood tests.
- you are known to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QT 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 Voriconazole Rowex:
- tell your doctor immediately if you develop
  - o sunburn
  - o severe skin rash or blisters
  - o 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 Voriconazole Rowex.

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

Children and adolescents
Voriconazole Rowex should not be given to children younger than 2 years of age.

Other medicines and Voriconazole Rowex
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.
- Some medicines, when taken at the same time as Voriconazole Rowex, may affect the way Voriconazole Rowex works or Voriconazole Rowex may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with Voriconazole Rowex 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 Voriconazole Rowex 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 Voriconazole Rowex 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 Voriconazole Rowex 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)
- Sulphonylureas (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 take Voriconazole Rowex 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 can NOT be taken at the same time as Voriconazole Rowex)
- 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).

Pregnancy and breast-feeding
Voriconazole Rowex must not be used during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while being treated with Voriconazole Rowex.
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.

Driving and using machines
Voriconazole Rowex 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.

Voriconazole Rowex contains sodium and sulfobutylether-β-cyclodextrin sodium
This medicine contains 228.7 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 11.4% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 3.4 g sulfobutylether-β-cyclodextrin sodium in each vial. If you have a kidney disease, talk to your doctor before you receive this medicine.

3 How to use Voriconazole Rowex

Always take 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 teenagers is as follows:

	Intravenous	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers 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.

Voriconazole Rowex 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 Voriconazole Rowex for prevention of fungal infections, your doctor may stop giving Voriconazole Rowex if you or your child develop treatment related side effects.

If a dose of Voriconazole Rowex has been forgotten
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 taking Voriconazole Rowex
Voriconazole Rowex treatment will continue for as long as your doctor advises, however duration of treatment with Voriconazole Rowex 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 Voriconazole Rowex 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 Voriconazole Rowex and see a doctor immediately
- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis.

Other side effects

Very common side effects (may affect more than 1 in 10 people) are:
- Visual impairment (change in vision including blurred vision, visual colour 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, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes.

Common side effects (may affect up to 1 in 10 people) are:
- 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 characterised 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 side effects (may affect up to 1 in 100 people) are:
- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea,

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 discolouration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response.

Rare side effects (may affect up to 1 in 1000 people) are:
- 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**:
- 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 Voriconazole Rowex (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As Voriconazole Rowex 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 Voriconazole Rowex 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: HPRA Pharmacovigilance; website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Voriconazole Rowex

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 label and carton after 'EXP'. The expiry date refers to the last day of that month.

Store below 30°C.

After reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C for the reconstituted solution.

After diluted solution for infusion:
Chemical and physical stability of the diluted solutions for infusion has been demonstrated for 3 h at 20°C to 30°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 to 8°C (in a refrigerator) unless reconstitution has taken place in controlled and validated aseptic conditions.

(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 Voriconazole Rowex contains
- The active substance is voriconazole. Each vial contains 200 mg powder for solution for infusion, equivalent to a 10 mg/ml solution when reconstituted as directed by your hospital pharmacist or nurse (see the information at the end of this leaflet).
- The other ingredient is sulfobutylether-β-cyclodextrin sodium.

What Voriconazole Rowex looks like and contents of the pack

Single use 25 ml colourless type I glass vials closed with lyophilisation rubber stopper and sealed with aluminium flip-off seal with plastic disc and is inserted in a carton.

Pack sizes:

1, 5, 10 vials with powder for solution for infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers
Marketing Authorisation Holder
Rowex Ltd., Bantry, Co. Cork, Ireland.

Manufacturers
Lek Pharmaceuticals d.d., Verovškova 57, 1526 Ljubljana, Slovenia.
Salutas Pharma GmbH, Sachsen-Anhalt, 39179 Barleben, Germany.

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

NL Voriconazol Sandoz 200 mg, poeder voor oplossing voor infusie
BE Voriconazol Sandoz 200 mg poeder voor oplossing voor infusie
BG Voriconazole Sandoz 200mg Powder for solution for infusion
CZ Vorikonazol Sandoz 200 mg prášek pro infuzní roztok
DE Voriconazol HEXAL 200 mg Pulver zur Herstellung einer Infusionslösung ENR 2189283
DK Voriconazole Sandoz
EL Voriconazole /Sandoz
IE Voriconazole Rowex 200 mg Powder for Solution for Infusion
HR Vorikonazol Sandoz 200 mg prašak za otopinu za infuziju
IT Voriconazolo Sandoz GmbH
NO Voriconazole Sandoz
PL Voriconazole Sandoz
SI Vorikonazol Sandoz 200 mg prašek za raztopino za infundiranje
SK Vorikonazol Sandoz 200 mg prášok na infúzny roztok

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The following information is intended for medical or healthcare professionals only:

Reconstitution and Dilution information
- Voriconazole Rowex powder for solution for infusion needs to first be reconstituted with either 19 ml of Water for Injections or 19 ml of 9 mg/ml (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml voriconazole.
- Discard the Voriconazole Rowex 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 9 mg/ml (0.9%) Sodium Chloride for Infusion is dispensed.
- The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final Voriconazole Rowex 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 Voriconazole Rowex'.

Required Volumes of 10 mg/ml Voriconazole Concentrate

Body Weight (kg)	Volume of Voriconazole 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)	-	-

Voriconazole Rowex is a single dose unpreserved sterile lyophilisate. 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 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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

9 mg/ml (0.9%) Sodium Chloride for Infusion
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 0.9% Sodium Chloride Intravenous Infusion

The compatibility of Voriconazole Rowex with diluents other than listed above (or listed below under 'Incompatibilities') is unknown.

Incompatibilities:
Voriconazole Rowex solution must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (e.g., Aminofusin 10% Plus).

Infusions of blood products must not occur simultaneously with Voriconazole Rowex.

Infusion of total parenteral nutrition can occur simultaneously with Voriconazole Rowex but not in the same line or cannula.

Voriconazole Rowex must not be diluted with 4.2% Sodium Bicarbonate Infusion.