

*Your doctor is the best resource for medical advice and information. The health information contained herein is provided for educational / awareness purposes only and is not intended to replace discussions with a medical practitioner and/or medical advice or be construed as a promotional information.*

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# Package Leaflet: Information for the user

## Voriconazole Tablets I.P. and

## Voriconazole Powder for Solution for

## Infusion I.P.

### VFEND<sup>TM</sup>

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**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- If you have any further questions, ask your doctor.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet:**

1. What VFEND (Voriconazole) is and what it is used for
2. What you need to know before you take VFEND (Voriconazole)
3. How to take/use VFEND (Voriconazole)
4. Possible side effects
5. How to store VFEND (Voriconazole)
6. Contents of the pack and other information

#### **1. What VFEND (Voriconazole) is and what it is used for**

VFEND (Voriconazole) contains the active substance voriconazole. VFEND (Voriconazole) is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is a broad spectrum, triazole antifungal agent and is used for following indications:

- Treatment of invasive aspergillosis;
- Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*);
- Treatment of oesophageal candidiasis;
- Treatment of serious fungal infection caused by *Scedosporium spp.* and *Fusarium spp.* including *Fusarium solani* in patients intolerant of or refractory to other therapy.

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- Candidemia in non-neutropenic patients and the following Candida infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.

## **2. What you need to know before you take VFEND (Voriconazole)**

### **Do not take VFEND (Voriconazole)**

If you are allergic to voriconazole or any of the other ingredients of this medicine (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 course of VFEND (Voriconazole) treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Ivabradine (used for symptoms of chronic heart failure)
- 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 400mg and more twice daily
- St. John's Wort (herbal supplement)
- Naloxegol (used to treat constipation specifically caused by pain medicines, called opioids, (e.g., morphine, oxycodone, fentanyl, tramadol, codeine))
- Tolvaptan (used to treat hyponatremia (low levels of sodium in your blood) or to slow kidney function decline in patients with polycystic kidney disease)
- Lurasidone (used to treat depression)
- Venetoclax (used to treat patients with chronic lymphocytic leukaemia-CLL)

### **Warnings and precautions**

Talk to your doctor before taking VFEND (Voriconazole) 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 VFEND (Voriconazole). Your doctor should also monitor your liver function while you are being treated with VFEND (Voriconazole) by doing blood tests.
- You are known to have cardiomyopathy, irregular heart beat, 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 VFEND (Voriconazole):

- 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 VFEND (Voriconazole).

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.

If you develop signs of 'Cushing's syndrome' where the body produces too much of the hormone cortisol which may lead to symptoms such as: weight gain, fatty hump between the shoulders, a rounded face, darkening of the skin on the stomach, thighs breasts, and arms, thinning skin, bruising easily, high blood sugar, excessive hair growth, excessive sweating, please tell your doctor.

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

### **Children and adolescents**

VFEND (Voriconazole) should not be given to children younger than 2 years of age.

### **Other medicines and VFEND (Voriconazole)**

Please 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 VFEND (Voriconazole), may affect the way VFEND (Voriconazole) works or VFEND (Voriconazole) may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with VFEND (Voriconazole) at the same time should be avoided if possible:

- Ritonavir (used for treating HIV) in doses of 100 mg twice daily
- Glasdegib (used for treating cancer) – if you need to use both drugs your doctor will monitor your heart rhythm frequently

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND (Voriconazole) 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 VFEND (Voriconazole) 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 VFEND (Voriconazole) 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 take VFEND (Voriconazole) 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)
- Tyrosine kinase inhibitors (e.g., axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) (used for treating cancer)
- Tretinoin (used to treat leukaemia)
- 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 VFEND (Voriconazole))
- 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)
- Letemovir (used for preventing cytomegalovirus (CMV) disease after bone marrow transplant)
- Ivacaftor: used to treat cystic fibrosis
- Flucloxacillin (antibiotic used against bacterial infections)

### **Pregnancy and breast-feeding**

VFEND (Voriconazole) must not be taken/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 taking/being treated with VFEND (Voriconazole).

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

## Driving and using machines

VFEND (Voriconazole) may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Contact/tell your doctor if you experience this.

## VFEND (Voriconazole) tablet contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, tell your doctor before taking VFEND (Voriconazole).

## VFEND (Voriconazole) contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 50 mg tablet, that is to say essentially 'sodium-free'.

This medicine contains less than 1 mmol sodium (23 mg) per 200 mg tablet, that is to say essentially 'sodium-free'.

This medicine contains 221 mg of sodium (main component of cooking/table salt) per vial. This is equivalent to 11% of the recommended maximum daily dietary intake of sodium for an adult.

## VFEND (Voriconazole) powder for solution for infusion contains cyclodextrins

This medicine contains 3,200 mg cyclodextrins in each vial which is equivalent to 160 mg/ml when reconstituted in 20 ml. If you have a kidney disease, talk to your doctor before you receive this medicine.

## 3. How to take/use VFEND (Voriconazole)

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.

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

	Tablets	
	Patients 40 kg and above	Patients less than 40 kg
<b>Dose for the first 24 hours</b> (Loading Dose)	400 mg every 12 hours for the first 24 hours	200 mg every 12 hours for the first 24 hours
<b>Dose after the first 24 hours</b> (Maintenance Dose)	200 mg twice a day	100 mg twice a day

Depending on your response to treatment, your doctor may increase the daily dose to 300 mg twice a day.

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

**Powder for solution for infusion:**

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

	<b>Intravenous</b>
<b>Dose for the first 24 hours</b> (Loading Dose)	6 mg/kg every 12 hours for the first 24 hours
<b>Dose after the first 24 hours</b> (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:

	<b>Tablets</b>	
	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
<b>Dose for the first 24 hours</b> (Loading Dose)	Your treatment will be started as an infusion	400 mg every 12 hours for the first 24 hours
<b>Dose after the first 24 hours</b> (Maintenance Dose)	9 mg/kg twice a day (a maximum dose of 350 mg twice daily)	200 mg twice a day

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

- Tablets must only be given if the child is able to swallow tablets.

Take your tablet at least one hour before, or one hour after a meal. Swallow the tablet whole with some water.

**Powder for solution for infusion:**

The recommended dose for children and teenagers is as follows:

	<b>Intravenous</b>	
	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
<b>Dose for the first 24 hours</b> (Loading Dose)	9 mg/kg every 12 hours for the first 24 hours	6 mg/kg every 12 hours for the first 24 hours
<b>Dose after the first 24 hours</b> (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.

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

**If you take more VFEND (Voriconazole) than you should**

If you take more tablets than prescribed (or if someone else takes your tablets) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of VFEND (Voriconazole) tablets with you. You may experience abnormal intolerance to light as a result of taking more VFEND (Voriconazole) than you should.

**If you forget to take VFEND (Voriconazole)**

It is important to take your VFEND (Voriconazole) tablets regularly at the same time each day. If you forget to take one dose, take your next dose when it is due. Do not take a double dose to make up for a forgotten dose.

**Powder for solution for infusion:****If a dose of VFEND (Voriconazole) 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 VFEND (Voriconazole)**

It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your medicine. Therefore unless your doctor instructs you to stop treatment, it is important to keep taking VFEND (Voriconazole) correctly, as described above.

Continue taking VFEND (Voriconazole) until your doctor tells you to stop. Do not stop treatment early because your infection may not be cured.

Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning.

### **Powder for solution for infusion:**

VFEND (Voriconazole) treatment will continue for as long as your doctor advises, however duration of treatment with VFEND (Voriconazole) 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 VFEND (Voriconazole) 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.

## **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 like:

- 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, diarrhoea
- 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
- Skin cancer

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 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, , 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 1000 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:

- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:

- 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 VFEND (Voriconazole) (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As VFEND (Voriconazole) 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 inform 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 VFEND (Voriconazole) 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.

## **5. How to store VFEND (Voriconazole)**

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

Store below 30°C.

### **Powder for solution for infusion:**

The unreconstituted vial should be stored below 30°C.

Once reconstituted, VFEND (Voriconazole) should be used immediately, but if necessary may be stored for up to 24 hours at 2°C - 8°C (in a refrigerator).

## **6. Contents of the pack and other information**

### **What VFEND (Voriconazole) contains**

- The active substance is voriconazole. Each tablet contains either 50 mg voriconazole (for VFEND 50 mg film-coated tablets) or 200 mg voriconazole (for VFEND 200 mg film-coated tablets).
- The other ingredients are lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate which make up the tablet core and hypromellose, titanium dioxide (E171), lactose monohydrate and glycerol triacetate which make up the film-coat (see section 2, VFEND 50 mg film-coated tablets or VFEND 200 mg film-coated tablets contains lactose and sodium).

### **Powder for solution for infusion:**

- The active substance is voriconazole.
- The other ingredient is sulfobutylether beta cyclodextrin sodium (see section 2).

Each vial contains 200 mg voriconazole, 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).

### **What VFEND (Voriconazole) looks like and contents of the pack**

#### **Film-coated tablets:**

VFEND (Voriconazole) 50 mg film-coated tablets are supplied as white round film-coated tablets with Pfizer marked on one side and VOR50 on the reverse.

VFEND (Voriconazole) 200 mg film-coated tablets are supplied as white capsule shaped film-coated tablets with Pfizer marked on one side and VOR200 on the reverse.

The tablets come in a mono carton containing a blister pack of 7 tablets.

#### **Blister pack:**

50 mg tablets: Blister pack made up of 250 microns transparent PVC and 25 microns hard tempered aluminium with vinyl-acrylate based heat seal coating on the bright side of the foil, 1.6 g/m<sup>2</sup> polyester based lacquer on the matt side.

200 mg tablets: Blister pack made up of 300 microns transparent PVC and 25 microns hard tempered aluminium with vinyl-acrylate based heat seal coating on the bright side of the foil, 1.6 g/m<sup>2</sup> polyester based lacquer on the matt side.

Not all pack sizes may be marketed.

**Powder for solution for infusion:**

Voriconazole powder for solution for infusion is a white lyophilised powder containing nominally 200 mg voriconazole in individually boxed, single use 30 ml clear Type I glass vials with rubber stoppers and aluminium caps with plastic seals.

**Manufactured by:**

Please refer to outer carton

*This leaflet was created based on LPD: LPDVRC122023;*