PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

VFEND® 50 mg
VFEND® 200 mg
Film-coated tablets

VFEND® 40 mg/ml
Powder for oral suspension

Film-coated tablets: Voriconazole 50 mg, 200 mg
Each ml of reconstituted suspension contains: Voriconazole 40 mg
A list of inactive ingredients and allergens in the preparation is in section 6.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.
This medicine is not intended for children and infants under the age of two years.

1.WHAT IS THIS MEDICINE INTENDED FOR?
VFEND® is an anti-fungal preparation. It works by killing or stopping the growth of different fungi that cause infections. The preparation is intended for patients with worsening, possibly even life-threatening, infections. In addition, the preparation serves to prevent fungal infections in bone marrow transplant patients who are at high risk.
The preparation should be used only under medical supervision.

Therapeutic group:
Anti-fungal from the triazole group.

2.BEFORE USING THE MEDICINE
Do not use the medicine if:

x You are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine, listed in section 6.
x Do not take this medicine with terfenadine (for allergy), astemizole (for allergy), cisapride (for stomach problems), pimozide (for mental problems), quinidine (for heart rate problems), rifampicin (for treating tuberculosis), carbamazepine (for treating seizures), phenobarbital (for treating seizures and severe insomnia), ergot derivatives (ergotamine, dihydroergotamine; for treating migraines), sirolimus (for transplant patients), efavirenz at a dosage of 400 mg and more once a day (for treating HIV), ritonavir at dosages given twice a day of 400 mg and more each time (for treating HIV), the Hypericum herb (St. John's Wort).

Before starting treatment with VFEND®, tell the doctor if:
- if you suffer, or have suffered in the past, from an allergic reaction to preparations from the azole group.
- if you suffer from cardiomyopathy or a heart rate impairment.
- if you suffer, or have suffered in the past, from a liver disease. Your doctor will monitor your liver function by performing blood tests.

Special warnings regarding use of the medicine
! Avoid any sun exposure while using the medicine. It is important to cover areas of the body that may be exposed to the sun and to use sunscreen with a high sun protection factor (SPF), as an increased sensitivity of the skin to the sun's rays may occur. This warning is also applicable to children.
! During use of the medicine, tell the doctor immediately if you get a sunburn, develop a severe skin rash or blisters, pain in the bones. If you develop one of these skin effects, your doctor may refer you to a dermatologist. There is a small chance of developing skin cancer upon long-term use of VFEND®.
! Your doctor will monitor liver and kidney function by performing blood tests during the course of treatment with VFEND®.
! Before starting and during the course of treatment, monitor for disturbances in electrolyte levels, such as hypokalemia, hypomagnesemia, hypocalcemia.

Tests and Follow-up
As VFEND® affects the liver and the kidney, your doctor should monitor the function of your liver and kidney by performing blood tests. Please tell your doctor if you experience abdominal pain or if your stools have a different consistency.

Other medicines and VFEND®
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular, if you are taking:
Medicines whose administration in combination with VFEND® should be avoided if possible and a dosage adjustment is required if given together:
- Phenytoin (to treat epilepsy). If you are taking this medicine, the blood level of phenytoin should be monitored.
- Ritonavir (to treat HIV) at a low dosage of 100 mg twice a day. Certain dosages of ritonavir can not be taken with VFEND®, see "Do not use the medicine if", in this section.
- Rifabutin (to treat tuberculosis). If you are being treated with rifabutin, you must perform a blood count and side effects to rifabutin should be monitored regularly.

Medicines that, when taken with VFEND®, may require a dosage adjustment and monitoring that the medicines and/or VFEND® are still having the desired effect:
- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol)
- Ciclosporin, tacrolimus (for transplant patients)
- Sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) (to treat diabetes)
- Statins (e.g., atorvastatin, simvastatin, lovastatin) (to treat high cholesterol level)
- Benzodiazepines (e.g., midazolam, alprazolam, and triazolam) (for severe insomnia and as a tranquilizer)
- Omeprazole (to treat peptic ulcers)
- Oral contraceptives
- Vinca alkaloids (e.g., vincristine and vinblastine) (to treat cancer)
- Indinavir and other HIV protease inhibitors (to treat HIV)
- NNRTI medicines to treat AIDS, e.g., delavirdine, nevirapine, efavirenz (some dosages of efavirenz can not be taken with VFEND®; see section "Do not use the medicine if" in this section)
- Methadone (to treat addiction)
- Short-acting opiates (e.g., alfentanil, fentanyl and sufentanil) (painkillers for surgical procedures)
- Oxycodone and hydrocodone (to relieve moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen and diclofenac) (to treat pain and inflammation)
- Fluconazole (to treat fungal infections)
- Everolimus (to treat advanced kidney cancer and in transplant patients)

Pregnancy and breastfeeding
Do not use this medicine if you are pregnant, unless you received an explicit instruction from the doctor. Women of childbearing age must use effective contraceptives when using the medicine. Refer to your doctor immediately if you become pregnant while taking VFEND®.
If you are pregnant or breastfeeding, think you are pregnant or are planning a pregnancy, refer to a doctor before taking the medicine.

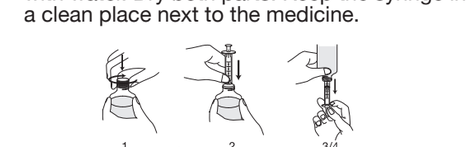
Driving and use of machinery
VFEND® may cause blurring of vision or sensitivity to light. If you are affected by it, do not drive or operate dangerous machinery. Children should be cautioned against riding a bicycle or playing near the road and the like.

Important information about some of the ingredients of VFEND®
The suspension contains sucrose; therefore, if you were told by a doctor that you have an intolerance to certain sugars, refer to a doctor before taking the medicine. The tablets contain lactose; therefore, if you have been told by a doctor that you have an intolerance to certain sugars, refer to a doctor before taking the medicine.

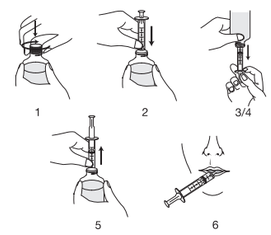
3.HOW SHOULD YOU USE THE MEDICINE?
Always use this preparation according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.
The dosage and treatment regimen will be determined by the doctor only. The dosage will be determined depending on your weight and the type of your infection.
Depending on your response to treatment, your doctor may increase or decrease your daily dosage.
Do not exceed the recommended dose!
If you or your child are taking VFEND® to prevent fungal infections, your doctor may stop the treatment if you or your child develop treatment-related side effects.
- Tablets should only be given if the child is capable of swallowing tablets.

Film-coated tablets: Take the tablet at least one hour before or one hour after a meal.
Swallow the tablet whole with a little water.
Do not crush/halve/chew, since the tablet is coated.
Suspension: Take the suspension at least one hour before or two hours after a meal.
Do not mix the suspension with any other medicine and do not dilute the reconstituted suspension with water or any other liquid.

Directions for preparation of the suspension:
The package contains a measuring cup intended for reconstitution by a pharmacist, a bottle adaptor, which will be attached by the pharmacist, and a syringe intended for the patient's use. The suspension is ready for use if it is in liquid form. If the powder looks dry, prepare the suspension according to the instructions below.
1. Tap the bottle to release the powder.
2. Remove the cap.
3. Add 2 measuring cups (a measuring cup is supplied in the carton) of water (total of 46 ml) to the bottle. Fill the measuring cup up to the marked line, then add the water to the bottle. Always add a total of 46 ml of water, regardless of the dosage you are taking.
4. Replace the cap and shake the bottle vigorously for one minute. After reconstitution, the total volume of the suspension must be 75 ml.
5. Remove the cap. Press the bottle adaptor into the neck of the bottle (as shown in the figure below). The adaptor is supplied to enable the filling of the syringe with medicine from the bottle. Replace the cap on the bottle.
6. Write the expiry date of the reconstituted suspension on the preparation labels.
Do not use the suspension beyond 14 days after reconstitution. Discard all remnants of the suspension after this date.



Instructions for use:
1. Shake the reconstituted suspension in the closed bottle for approximately 10 seconds before each use. Remove the cap.
2. Place the bottle on a flat surface and insert the tip of the syringe into the hole in the bottle adaptor.
3. Turn the bottle upside down while holding the syringe in place. Slowly pull back the plunger of the syringe to the graduation mark appropriate for your dose. The top edge of the black ring should be lined up with the proper dosage marked on the syringe.
4. If you notice large bubbles, slowly push the plunger of the syringe back into the syringe, so that the suspension of the medicine is returned to the bottle. Repeat step no. 3.
5. Turn the bottle back upright with the syringe still in place. Remove the syringe.
6. Put the tip of the syringe into your mouth. **Slowly** push down on the plunger of the syringe to instill the suspension into your mouth (toward the inner cheek). Do not push quickly to eject the medicine. If the suspension is given to a child, make sure the child is sitting, or is held upright before administration.
7. Close the bottle with the cap; the bottle adaptor remains in place.
8. Wash the syringe after each use. Clean both parts of the syringe in soapy water and rinse with water. Dry both parts. Keep the syringe in a clean place next to the medicine.



If you accidentally took a higher dosage
If you took an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room, and bring the package of the medicine with you. You may experience increased sensitivity to light as a result of taking an overdose.

If you forget to take the medicine
It is important that you take the medicine at the same time every day.
If you forgot to take the medicine at the required time, take the next dose at the scheduled time, but never take a double dose to compensate for a forgotten dose.
Adhere to the treatment regimen recommended by the doctor.
Even if there is an improvement in your health condition, do not stop treatment with the medicine without consulting a doctor.

If you stop taking the medicine
If you stop taking the medicine early, your infection may continue or recur.
Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4.SIDE EFFECTS
As with any medicine, use of the medicine may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Serious side effects - stop taking the medicine and refer to the doctor immediately
- Rash
- Jaundice and/or change in blood test results for liver function
- Pancreatitis

Additional side effects
Very common side effects (may occur in more than 1 in 10 people):
- Visual impairment (change in vision including blurred vision, color alterations, increased sensitivity to light, color blindness, eye disorder, halo, night blindness, swinging vision, seeing sparks, aura, reduced visual acuity, blinding brightness, narrowed field of vision, blotches/spots in the field of vision)
- Fever
- Rash
- Nausea, vomiting, diarrhea
- Headache
- Swelling in the extremities
- Stomach pain
- Breathing difficulties
- Increased liver enzymes

Common side effects (may occur in up to 1 in 10 people):
- Sinusitis, inflammation of the gums, chills, weakness
- Low level, including severe, of certain red and/or white blood cells (sometimes accompanied by fever), low level of platelets that help the blood to clot
- Low blood sugar level, low blood potassium level, low blood sodium level
- Anxiety, agitation, depression, confusion, sleep difficulties, hallucinations
- Seizures, tremor or involuntary muscle movement, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast/very slow heartbeat, fainting
- Low blood pressure, inflammation of the veins (which may be associated with the formation of a blood clot)
- Acute breathing difficulties, chest pain, swelling of the face (mouth, lips and around the eyes), fluid retention in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver (hepatitis) and liver damage
- Skin rashes which may lead to severe peeling and blistering of the skin characterized by a flat red area on the skin 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 occur in up to 1 in 100 people):
- Feeling sick, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing diarrhea, inflammation of the lymphatic system
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal cavity
- Enlarged lymph glands (sometimes painful), failure of bone marrow, increased eosinophil level in the blood
- Decreased function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning sensation in the limbs
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and/or inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve causing vision disturbance, optic disc swelling
- Decreased sensitivity to touch
- Change in sense of taste
- Hearing disturbances, ringing in the ears, vertigo (dizzy sensation)
- Inflammation of certain internal organs - pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallstones or gallbladder disease
- Joint inflammation, inflammation of the veins (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, protein in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes accompanied by irregular electric impulses
- Changes in the electrocardiogram (E.C.G)
- Increase in level of blood cholesterol, increased level of blood urea
- Allergic skin reactions (sometimes severe), including life-threatening conditions of the skin, which cause onset of painful blisters, sores/warts on the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reactions as a result of exposure to light or sun, skin redness and irritation, red or purple spots on the skin due to a decrease in the blood platelet count, eczema
- Allergic reaction or abnormal immune response

Rare side effects (may occur in up to 1 in 1,000 people):
- Overactive thyroid gland
- Deterioration of brain function (a serious complication of liver disease)
- Severe damage to the optic nerve, cloudy cornea, involuntary eye movement
- Appearance of blisters as a result of sensitivity/exposure to light
- 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 (edema) of the skin, itchy or sore patches of thick, red skin with scales, itching of the skin and mucous membranes, a 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 and scaly skin patches, sometimes thick with 'horns'

Side effects of unknown frequency (effects whose frequency has not been determined):
- Freckles and pigmented spots

Side effects of unknown frequency (effects whose frequency has not been determined), but are significant and need to be reported to the attending doctor immediately:
- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red and scaly areas or ring-shaped skin lesions, may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

There have been reports of skin cancer developing in patients treated with VFEND® for long periods of time.
Sunburn or a severe skin reaction, following exposure to light or sun, was observed more frequently in children. If you/your child develop skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide whether it is important for you/your child to come for monitoring on a regular basis.
An increase in liver enzymes has also been observed more frequently in children.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor. Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il/

5.HOW SHOULD THE MEDICINE BE STORED?
- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- **Storage conditions:**
Film-coated tablets - store in a cool place.
Suspension - before preparation (reconstitution): store the powder in the refrigerator (2°-8°C).
after preparation (reconstitution): store the reconstituted suspension below 30°C (do not store in a refrigerator or freezer) and use it within 14 days from the preparation day.

6.FURTHER INFORMATION
In addition to the active ingredient, the medicine also contains:
Film-coated tablets:
Lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone, magnesium stearate, hypromellose, titanium dioxide, glycerol triacetate.

Suspension:
Sucrose, citric acid (anhydrous), natural orange flavour, sodium citrate dihydrate, sodium benzoate, xanthan gum, silica colloidal anhydrous, titanium dioxide.

The tablets contain lactose monohydrate:
VFEND® 50 mg: 62.5 mg.
VFEND® 200 mg: 250 mg.

The suspension contains sucrose:
Each ml of reconstituted suspension contains: 0.54 grams of sugar.

What the medicine looks like and the contents of the package:
VFEND® 50 mg film-coated tablets: white to off-white round tablet marked with "Pfizer" on one side and "VOR 50" on the other side.
VFEND® 200 mg film-coated tablets: white to off-white oval-shaped tablet marked with "Pfizer" on one side and "VOR 200" on the other side.
The medicine comes in a package of 2, 10, 14, 20, 28, 30, 50, 56, 100 tablets.
Not all package sizes may be marketed.
VFEND® 40 mg/ml powder for oral suspension: white to off-white powder for preparing a white to off-white, orange-flavored suspension.
The suspension comes in a 75 ml bottle.

License holder: Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

Manufacturer: Film-coated tablets: R-PHARM, Illertissen, Germany
Suspension: Fareva Amboise, Poce-sur-Cisse, France

This leaflet was checked and approved by the Ministry of Health in May 2017 and was updated in accordance with the Ministry of Health guidelines in March 2019.
Registration number of the medicine in the National Drug Registry of the Ministry of Health:
VFEND® 50 mg film-coated tablets: 126.69.30596
VFEND® 200 mg film-coated tablets: 126.70.30597
VFEND® 40 mg/ml powder for oral suspension: 134.48.31157