PATIENT INFORMATION LEAFLET

VORİKANDİN 200 mg powder for solution for i.v. infusion

For intraveineuse administration.

Sterile

- ***Active Substance:*** 200 mg voriconazole. Each mL contains 10 mg voriconazole after reconstitution.
- ***Excipients:*** Sulfobutyl ether beta cyclodextrin sodium (SBECD), water for injection.

Before using this medicine, read all of this PATIENT INFORMATION LEAFLET carefully. Because, this leaflet includes important information for you.

- *Keep this PATIENT INFORMATION LEAFLET. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you. Do not pass it on to others.*
- *During the use of this medicine, tell that you are using this medicine when you go to a doctor or hospital.*
- *Follow these instructions exactly as written. Do not use* ***higher or lower*** *dose other than your recommended dose.*

In this leaflet:

headlines are included.

1. What is VORİKANDİN and what is it used for?

VORİKANDİN 200 mg white powder for solution for I.V infusion contains 200 mg voriconazole. It is available in single use glass vials. When reconstituted each ml contains 10 mg voriconazole.

VORİKANDİN belongs to a group of drugs called triazole used against fungal infections (antifungal). These drugs are used to treat a wide variety of fungal diseases. VORİKANDİN works by killing or stopping the growth of the fungi that cause infections.

VORİKANDİN is used for the treatment of adults and children over the age of 2 with:

- Serious fungal infections caused by *Aspergillus, Scedosporium, Fusarium* and fluconazole-resistant *Candida*

- Fungal infection of the blood (candidaemia) in patients with normal white blood cells count.

This product should only be used under the supervision of a doctor. VORİKANDİN is mainly used in patients with severe disease.

2. Before you are given VORİKANDİN

DO NOT USE VORİKANDİN under the following circumstances

- If you are allergic to voriconazole, or to any of the other ingredients of VORİKANDİN.

Inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Some drugs and VORİKANDİN may interfere with each other.

It must not be used for children under the ages of 2 years.

The list of drugs that may interact with VORİKANDİN is given in the section "VORİKANDİN with other drugs". However, you should not use VORİKANDİN if you are taking the medicines in the following list:

- 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
- Rifampicin used for treating tuberculosis
- Efavirenz used for treating HIV (in doses of 400mg and above once daily)
- Carbamazepine used to treat seizures (epilepsy)
- 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).
- Rifabutin (should not be used concomitantly if the expected benefit is not greater)

USE VORİKANDİN with CAUTION

If,

- you have had an allergic reaction to other azoles (i.e. fluconazole),
- you are known to have a heart related muscle disease (cardiomyopathy), irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called "QT prolongation",

- Your blood potassium, magnesium and calcium levels are below normal (if you have electrolyte disorder),
- If you are taking medication known to prolong the QT interval (eg quinidine, procaineamide),
- You have long lasting visual impairment such as blurred vision, inflammation of the visual nerve and eye ground edema
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VORİKANDİN. Your doctor should also monitor your liver function while you are being treated with VORİKANDİN by doing blood tests.
- You are suffering from kidney disease. Your doctor will monitor the function of your kidney by doing blood tests.
- There is a risk of non-chronic pancreatitis (acute pancreatitis), you have recently received cancer medication (chemotherapy), stem cell transplantation

You should avoid any sunlight and sun exposure while being treated. Cover sun exposed areas of skin and use sunscreen, 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 VORİKANDİN:

Tell your doctor immediately

- if you develop sunburn,
- severe skin rash, itching or blisters,
- Photosensitive skin reaction,
- Bone pain.
- Life-threatening skin conditions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, progressing through the separation of blisters and skin layers in the skin
- A severe skin reaction with symptoms such as rash, fever, swollen lymph nodes, and increased eosinophils (a type of white blood cell) known as DRESS syndrome.

There is a small chance that skin cancer could develop with long-term use of VORİKANDİN.

Your doctor should monitor the function of your liver and kidney by doing blood tests while you are treated with VORİKANDİN.

If these warnings apply or applied to you, please consult your physician.

Using VORİKANDİN with food and drink

Not important with regard to the route of administration.

Pregnancy

Please consult your physician or pharmacist before taking the drug.

VORİKANDİN should not be used in pregnant women unless deemed necessary by the doctor.

Women with childbearing potential should use effective birth control methods.

If you realize that you are pregnant during your treatment, immediately consult your physician or pharmacist.

Lactation

Please consult your physician or pharmacist before taking the drug.

VORİKANDİN should not be used when breastfeeding. Consult your doctor before taking any medicine.

Ability to drive and use machines

VORİKANDİN may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Avoid driving or operating dangerous machines in the event these changes occur. Driving at night is not recommended while using voriconazole.

Vital information regarding some of the excipients contained in VORİKANDİN

This medicinal product contains 217.6 mg sodium per vial. The sodium content should be taken into account in patients on a controlled sodium diet.

Use in combination with other drugs

Inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Dose adjustment or monitoring may be required to confirm the desired effect.

Some drugs and VORİKANDİN may reciprocally affect their mechanism of action when taken at the same time.

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

- Ritonavir used for treating HIV in doses of 100mg twice daily
- 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 VORİKANDİN and your dose may be adjusted.
- 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 VORİKANDİN 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
- Medicines e.g. efavirenz, delavirdine, nevirapine used for treating HIV (some doses of efavirenz can not be taken at the same time as VORİKANDİN)
- Methadone used to treat heroin addiction
- Efavirenz used for treating HIV (some doses of efavirenz can not be taken at the same time as VORİKANDİN)
- 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
- Fluconazole used for fungal infections
- Non-steroidal anti-inflammatory drugs e.g. ibuprofen, diclofenac, used for treating pain and inflammation
- Everolimus used for treating advanced kidney cancer and in transplant patients.

If you are currently taking or recently took any prescribed or over-the-counter drugs, please inform your physician or pharmacist.

3. How you will be given VORİKANDİN?

Instructions regarding correct use and dosage/administration frequency:

Always use VORİKANDİN as your doctor has told you. Check with your doctor or pharmacist 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 twice daily (per 12 hours)
Dose after the first 24 hours (Maintenance dose)	4 mg/kg twice daily (per 12 hours)

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

Route and method of administration:

For intravenous use.

VORİKANDİN Powder for Solution for Infusion will be diluted and reconstituted by your pharmacist or nurse.

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

Various age groups:

Use in children:

The recommended dose for children and teenagers is as follows:

	Intravenous	
	Children aged 2 to 12 years and teenagers aged 12 to 14 years weighing less than 50kg	**Teenagers aged 12 to 14 years weighing 50kg 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 daily	4 mg/kg twice daily

VORİKANDİN should not be given to children under the age of 2.

In elderly:

Your doctor will not make a special dose adjustment for you.

Special usage cases:

Renal failure:

If you have kidney failure, your doctor will decide the use of this medicine.

Hepatic failure:

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

Voriconazole has not been studied in patients with serious hepatic cirrhosis.

If you are under the impression that the effect VORİKANDİN is too strong or weak, consult your physician or pharmacist.

If you have taken more VORİKANDİN than you should have:

As you will be given this medicine under close medical supervision, it is unlikely that you would use more than required. If you think that you have been given an overdose, tell your doctor or pharmacist.

If you have used VORİKANDİN more than you should have or more than prescribed consult a physician or a pharmacist.

If you forget to take VORİKANDİN:

As you will be given this medicine under close supervision, it is very unlikely that you will miss a dose.

If you think that you have missed a dose, tell your doctor or pharmacist.

Do not double-dose to make up for forgotten doses.

Possible effects once VORİKANDİN treatment is concluded

VORİKANDİN treatment will continue for as long as your doctor advises. However duration of treatment 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 treatment with VORİKANDİN is stopped by your doctor you should not experience any effects.

4. Possible side effects

Like all medicines VORİKANDİN may cause side effects in patients sensitive to its ingredients.

The side effects that may occur are usually minor and temporary. However, some may be serious and need medical attention.

Side effects are listed as defined by following categories:

Very common : may be seen in at least one of 10 patients;

Common	: may be seen in less than one of 10 patients but more than one of 100 patients;
Uncommon	: may be seen in less than one of 100 patients but more than one of 1000 patients.
Rare	: may be seen in less than one in 1,000 patients but more than one in 10,000 patients;
Very rare	: may be seen in at least one in 10,000 patients;
Not known	: Cannot be estimated from the available data.

If any of the following reactions happen, stop taking VORİKANDİN and tell your doctor immediately or contact the casualty department at your nearest hospital:

- Rash
- Jaundice; change in liver function tests
- Pancreatitis manifested by severe pain in the upper abdomen, nausea and vomiting
- Allergic reactions (anaphylactic reactions) characterized by fever, swelling in the mouth, swelling of the face, tongue and lips, shortness of breath, itching, skin rashes, and sometimes low blood pressure.

These are all very serious side effects.

These very serious side effects are all rare.

Other side effects:

Very common:

- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, color 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
- Abdominal pain
- Breathing difficulties
- Increased liver enzymes

Common:

- 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
- Allergic reaction or exaggerated immune response
- 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
- Itching
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon:

- 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, manifested by some or all of the symptoms: fever, vomiting, weakness, chills, swelling of the abdomen, drop in urine, diarrhea or constipation, hardening of the stomach
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil (type of allergy cell)
- Depressed function of the adrenal gland, underactive thyroid gland manifested by weight loss, nausea and loss of appetite, muscle and joint pain, darkening of skin color
- Abnormal brain function, Parkinson-like symptoms (i.e joint stiffness), nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain manifested by headache, dizziness, nausea

- 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 impulse
- 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 reactions or severe immune system response

Rare:

- Overactive thyroid gland (hyperthyroidism) manifested by weight loss, weakness in muscles, tremors in hands, difficulty in sleeping, palpitations, hair thinning and shedding, skin thinning, moistness and excessive sweating, increased bowel movements and sometimes diarrhea, irritability, bulging eyes
- Deterioration of brain function that is a serious complication of liver disease manifested by mental state disorder, neuromuscular abnormalities, tremor, faster and deeper breathing.
- 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 (Guillain-Barre Syndrome)
- 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 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
- A severe skin reaction known as DRESS syndrome (symptoms: rash, fever, swelling of the lymph nodes, and increased eosinophils (a type of white blood cell))

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, skin redness and hotness, limited function
- Red, scaly patches or ring-shaped skin lesions (called cutaneous lupus erythematosus)

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

As VORİKANDİN 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 VORİKANDİN 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.

Elevated liver enzymes were also observed more frequently in children.

If you notice any side effect not mentioned in this leaflet, please inform your doctor or pharmacist.

5. How to store VORİKANDİN

Keep VORİKANDİN out of the sight and reach of children, and in its original packaging

Use in compliance with the expiry date.

Do not use VORİKANDİN after the expiration date printed on its packaging. If you notice any irregularities in the product and/or its packaging, do not use VORİKANDİN.

VORİKANDİN Powder for Solution for I.V Infusion is stored at below 25°C.

VORİKANDİN powder should be used immediately after dissolution. If not used immediately, it can be stored at 2°C - 8°C (refrigerated) for up to 24 hours. Reconstituted powder needs to be further diluted with a compatible infusion solution. (Please refer to the end of this leaflet for further information)

Do not throw away drugs that have expired or are not used! Deliver to the collection system determined by local regulations.

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FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY

Reconstitution and Dilution information

- VORİKANDİN 200 mg I.V Powder for Solution for Infusion needs to first be reconstituted with either 19ml of Water for Injections or 19ml of 9mg/ml (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20ml of clear concentrate containing 10mg/ml voriconazole.
- Discard the voriconazole vial if vacuum does not pull the diluent into the vial.
- It is recommended that a standard 20 ml syringe be used to ensure that 19.0 ml of water for injections or 9 mg/ml Sodium Chloride for Infusion is dispensed.
- For administration, the required volume of the reconstituted concentrate is added to a recommended compatible infusion solution (detailed in the table below) to obtain a final VORİKANDİN solution containing 0.5-5 mg/ml.
- This product is for single use only, any unused solution should be discarded. Only clear colourless solutions without particles should be used.
- Not for bolus injection.
- For storage information, please refer to Section 5 'How to store VORİKANDİN.

Required Volumes of 10 mg/ml VORİKANDİN Concentrate

Body weight (kg)	Volume of VORİKANDİN Concentrate (10 mg/ml):				
	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)	-	-

VORİKANDİN 200 mg I.V Powder for Solution for Infusion is a sterile single-dose lyophilized without preservative. From a microbiological point of view, the product should be used immediately. If it is not to be used immediately, it is the user's responsibility to store the ready-to-use solution within storage times and conditions before use and cannot normally be stored for longer than 24 hours at 2°C-8°C unless the reconstitution is performed at a place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

Sodium Chloride 0.9 % for Injection

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

Incompatibilities

VORİKANDİN must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (i.e. 10% Aminofusin Plus).

Infusions of blood products must not occur simultaneously with VORİKANDİN.

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

VORİKANDİN must not be diluted with 4.2% sodium bicarbonate infusion.