PATIENT INFORMATION LEAFLET

TROZASİN 200 mg Powder for Solution for IV Infusion
Sterile- Apyrogen

For intravenous application

- ***Drug substance:*** Each vial contains 200 mg of voriconazole.
- ***Excipient(s):*** Hydroxypropyl-β-cyclodextrin and water for injection

Read all of this LEAFLET carefully before you start using this medicine because it contains important information for you.
- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you. Do not pass it on to others.*
- *During the use of this drug, tell your doctor that you are using this medication when you go to the doctor or hospital.*
- *Please keep strictly to write in these instructions. Do not use **high or low** dose outside the recommended dose of drug.*

In this leaflet:

1. What TROZASİN is and what it is used for

TROZASİN 200 mg Powder for Solution for IV Infusion contains 200 mg ofvoriconazole. It is available in single-use glass vials. After reconstitution, each milliliter contains 10 mg voriconazole.

TROZASİN is involved in a group of drugs called triazol (antifungal) which are used against fungal infections. These drugs are used to treat a wide variety of fungal diseases.. TROZASİNworks by killing or stopping the growth of the fungi that cause infections.

TROZASİN is used in (adults and children over the age of 2) :

- Treatment of severe fungal infections caused by *Aspergillus*, *Scedosporium*, *Fusarium* and fluconazole resistant *Candida*
- Treatment of fungal infections (candidiasis) in patients with normal white blood cell counts.

This product should only be used under the supervision of a doctor. TROZASİN is intended for patients with several infections.

2. What you need to know before you take TROZASİN ?

DO NOT take TROZASİN:

- If you are allergic to the active ingredient voriconazole, or to one of the other components contained in the TROZASİN.
- If you have severe renal insufficiency with creatinine clearance below 30ml / min.

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. Some medicines and TROZASİN may affect each other.

A list of medicines that can interact with TROZASİN is given in the section " Other medicines and TROZASİN".

However, if you use medications listed below, you should not use TROZASİN:

- 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 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)
- Rifabutin (must not be used with rifabutin unless the expected benefit is more)

Use TROZASİN CAREFULLY in following situations:

If:

- you have had an allergic reaction to other azoles (eg. Fluconazole).
- you are known to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.
- potassium, magnesium and calcium blood levels are below normal (if you have electrolyte impairment)
- you are taking medication known to prolong QT interval (eg quinidine, procainamide)
- you have a long-standing complaint such as vision-related blurred vision, inflammation of the optic nerve and papilledema,
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of TROZASİN. Your doctor should also monitor your liver function while you are being treated with TROZASİN by doing blood tests.
- you have any discomfort about your kidneys. Your doctor will monitor your kidney function by doing blood tests.
- there is a risk of non-chronic pancreatitis (acute pancreatitis), if you recently received cancer drug treatment (chemotherapy), if the stem cell transplant was done,

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 TROZASİN:
Tell your doctor immediately if you develop

- sunburn
- severe skin rash or blisters
- light sensitive intracutaneous reactivity
- 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 TROZASİN**.**

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

Please consult your doctor if these warnings available to you, even at any time in the past.

Use of TROZASİN with food and drink
It is not important with related to the administration route.

Pregnancy
Consult your doctor or pharmacist before using this medication.

TROZASİN should not be used in pregnant women unless prescribed by a doctor.

Women of child-bearing potential must always use effective contraception during treatment.

If you notice that you are pregnant during your treatment, consult your doctor or pharmacist immediately.

Breast-feeding
Consult your doctor or pharmacist before using this medication.

TROZASİN should not be used during breastfeeding. Consult your doctor before taking any medication.

Effects on ability to drive and use machines
TROZASİN can cause visual changes including blurring, change / increase in visual sense and / or photosensitivity when seeing transiently and reversibly. Avoid using cars or dangerous machinery in case these changes occur. It is not recommended to use the car at night when using TROZASİN.

Important information about some excipients in the content of TROZASİN
Because of the safety risks of the long-term use of the excipient hydroxypropyl-β-cyclodextrin, it is necessary to determine the physician should make the necessary evaluation after 21 days of use and whether the use should be continued or not.

Other medicines and TROZASİN

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 TROZASİN, may affect the way TROZASİN works or TROZASİN may affect the way they work.

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

- Ritonavir (used for treating HIV) in doses of 100 mg 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 TROZASİN 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 TROZASİN 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 TROZASİN)
- 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)
- 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)

Please inform your doctor or pharmacist if you are using or have recently used any medicine with or without prescription.

3. How to use TROZASİN

Instructions for proper usage and dosage/administration frequency:

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
The hydroxypropyl-beta-cyclodextrin present in the form of the intravenous form of TROZASİN is eliminated by glomerular filtration. For this reason, the use of TROZASİN I.V is contraindicated in patients with severe renal insufficiency with creatinine clearance below 30 ml / min.

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 a day
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.

Administration route and method:
It is used intravenously.

TROZASİN 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.

Different age groups:
Use in children:

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

TROZASİN should not be given to children younger than 2 years of age.

Use in elderly:
Your doctor will not adjustment special dose for you.

Special use cases:

Renal insufficiency:
When hydroxypropylbetadex is administered intravenously, it is removed by glomerular filtration. For this reason, the use of TROZASİN I.V is contraindicated in patients with severe renal insufficiency with creatinine clearance below 30 ml / min.

Liver insufficiency:
If you have mild to moderate cirrhosis, your doctor may decide to reduce your medication dose.
Voriconazole has not been studied in patients with severe liver cirrhosis.

If you have an impression that the effect of TROZASİN is too strong or weak, talk to your doctor or pharmacist.

If you take more TROZASİN than you should
As you will be given this medicine under close medical supervision, it is unlikely that you will use it more than you need to. However, tell your doctor or pharmacist if you think you are overdose.

If a dose of TROZASİN 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.

Do not take double doses to balance the forgotten dose.

If you stop taking TROZASİN
TROZASİN treatment will continue for as long as your doctor advises, however duration of treatment with TROZASİN Powder for Solution for Infusion should be no more than 6 months.

Patients with a weak 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 TROZASİN treatment is stopped by your doctor you should not experience any

effects.

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.

Side effects are ordered according to below categorization:

Very common	: at least 1 in 10 patients.
Common	: less than 1 in 10 patients, but, more than 1 in 100 patients
Uncommon	: less than 1 in 100 patients, but, more than 1in 1000 patients.
Rare	: less than 1in 100 patients, more than 1 in 10000 patients.
Very rare	: less than 1 in 10.000 patients.
Not-known	: It is not estimated from available data.

If you notice any of the following, stop using TROZASİN and contact a doctor IMMEDIATELY:

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis identified by severe pain, nausea and vomiting in the upper abdomen

All of these are very serious side effects.
All of these very serious side effects are very rare.

Other side effects

Very common:

- 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:

- Inflammation of the gastrointestinal tract, 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
- Itchiness
- 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 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 discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction

Rare:

- Increased thyroid hormone secretation (hyperthyroidism) in the body, weight loss, weakness in muscles, tremors in hands, difficulty in sleeping, palpitation, hair thinning and loss, thinning of skin, moistness and excessive sweating, increase in bowel movements, sometimes diarrhea, protruding eyes
- Deterioration of brain function that is a serious complication of liver disease symptoms like mental disorder, neuromuscular abnormalities, tremor, faster and deeper breathing
- Loss of most fibres 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 (E.g., multiple sclerosis)
- 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 TROZASİN (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As TROZASİN 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 TROZASİN 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.

If you notice other side effects which are not described in this patient information leaflet, inform your doctor or pharmacist.

Reporting of side effects
If you feel any side effects not listed in this leaflet talk to a doctor, pharmacist or nurse. Furthermore report the side effects you feel by clicking "Reporting Medicine Side Effect" in www.titck.gov.tr or by calling 0 800 314 00 08 side effect report line Turkey Pharmacovigilance Center. By reporting side effects, you can help provide more information on the safety of this medicine

5. How to store TROZASİN

Keep out of the reach and sight of children and store in the package.

Use in accordance with expiry date.
Do not use TROZASİN after the expiry date which is stated on the label.

TROZASİN 200 mg Powder for Solution for IV Infusion is stored at room temperature below 25°C.

Once reconstituted, TROZASİN should be used immediately, but if necessary may be stored for up to 24 hours at 2°C - 8°C (in a refrigerator). Reconstituted TROZASİN needs to be diluted with a compatible infusion solution first before it is infused. (Please refer to the end of this leaflet for furtherinformation).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer require.

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THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

Reconstitution and Dilution Information

- TROZASİN 200 mg Powder for Solution for IV Infusion needs to first be reconstituted with either 19 ml of Water for Injection 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 TROZASİN 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 TROZASİN solution containing 0.5 to 5 mg/ml of TROZASİN.

- 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 TROZASİN'.

Required Volumes of 10 mg/ml TROZASİN Concentrate

Body Weight (kg)	Volume of TROZASİN 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)	-	-

TROZASİN 200 mg Powder for Solution for IV Infusion is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the reconstituted solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

Sodium Chloride 9 mg/ml (0.9 %) Solution for Injection
Sodium Lactated IV Infusion
5 % Glucose and Lactated Ringer's Intravenous Infusion
5 % Glucose and 0.45% Sodium Chloride Intravenous
5 % Glucose Intravenous Infusion
5 % Glucose and 0.9 % Sodium Chloride Intravenous Infusion

Incompatibilities
TROZASİN 200 mg Powder for Solution for Infusion 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 applied simultaneously with TROZASİN 200 mg powder for solution for infusion.

Infusion of total parenteral nutrition can be applied simultaneously with TROZASİN 200 mg Powder for Solution for Infusion, but not in the same line or cannula.

TROZASİN 200 mg Powder for Solution for Infusion must not be diluted with 4.2 % Sodium Bicarbonate Infusion.