Package leaflet: Information for the user

Voriconazole Fresenius Kabi 200 mg powder for solution for infusion

Voriconazole

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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Voriconazole Fresenius Kabi 200 mg powder for solution for infusion; in the rest of the leaflet it will be called "Voriconazole Fresenius Kabi".

What is in this leaflet

1. What Voriconazole Fresenius Kabi is and what it is used for

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

It is used for the treatment of patients (adults and children over the age of 2) with:
- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp*),
- candidaemia (another type of fungal infection due to *Candida sp*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp*. (two different species of fungi).

Voriconazole Fresenius Kabi is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be used under the supervision of a doctor.

2. What you need to know before you use Voriconazole Fresenius Kabi

Do not use Voriconazole Fresenius Kabi:
- if you are allergic to the active ingredient 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 Voriconazole Fresenius Kabi 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)
- Rifampicin (used for treating tuberculosis)
- Efavirenz (used for treating HIV) in doses of 400 mg and above once daily
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Ritonavir (used for treating HIV) in doses of 400 mg and more twice daily
- St. John's Wort (herbal supplement)

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Voriconazole Fresenius Kabi.

Talk to your doctor before taking Voriconazole Fresenius Kabi if:

- you have had an allergic reaction to other azoles.
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of Voriconazole Fresenius Kabi. Your doctor should also monitor your liver function while you are being treated with Voriconazole Fresenius Kabi 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 sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with Voriconazole Fresenius Kabi :

- 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 Voriconazole Fresenius Kabi .

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

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

Other medicines and Voriconazole Fresenius Kabi
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines, when taken at the same time as Voriconazole Fresenius Kabi, may affect the way Voriconazole Fresenius Kabi works or Voriconazole Fresenius Kabi may affect the way they work.

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

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

Tell your doctor if you are taking either of the following medicines, as treatment with Voriconazole Fresenius Kabi at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:

- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin your blood counts and side effects to rifabutin will need to be monitored.
- Phenytoin (used to treat epilepsy). If you are already being treated with phenytoin your blood concentration of phenytoin will need to be monitored during your treatment with Voriconazole Fresenius Kabi and your dose may be adjusted.

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or Voriconazole Fresenius Kabi are still having the desired effect:

- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (e.g., tolbutamide, glipizide, and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g., midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take Voriconazole Fresenius Kabi whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as Voriconazole Fresenius Kabi)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

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

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

Driving and using machines
Voriconazole Fresenius Kabi may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Tell your doctor if you experience this.

Voriconazole Fresenius Kabi contains sodium
This medicinal product contains up to 3 mmol (or 69 mg) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Voriconazole Fresenius Kabi

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will determine your dose depending on your weight and the type of infection you have.
Your doctor may change your dose depending on your condition.

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

	Intravenous
Dose for the first 24 hours (Loading Dose)	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4 mg/kg twice a day

Depending on your response to treatment, your doctor may decrease the dose to 3 mg/kg twice daily.
The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents

The recommended dose for children and teenagers is as follows:

	Intravenous	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	9 mg/kg every 12 hours for the first 24 hours	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	8 mg/kg twice a day	4 mg/kg twice a day

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

Voriconazole Fresenius Kabi will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information).

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

If you or your child are taking Voriconazole Fresenius Kabi for prevention of fungal infections, your doctor may stop giving Voriconazole Fresenius Kabi if you or your child develop treatment related side effects.

If a dose of Voriconazole Fresenius Kabi 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, pharmacist or nurse if you think that a dose has been forgotten.

If you stop taking Voriconazole Fresenius Kabi
Voriconazole Fresenius Kabi treatment will continue for as long as your doctor advises, however duration of treatment with Voriconazole Fresenius Kabi should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long term treatment to prevent the infection from returning. You may be switched from the intravenous infusion to tablets once your condition improves.

When Voriconazole Fresenius Kabi treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects – Stop taking Voriconazole Fresenius Kabi and see a doctor immediately

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common side effects (may affect more than 1 in 10 people) are:

- Visual impairment (change in vision)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulites.

Common side effects (may affect up to 1 in 10 people) are:

- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types of red or white blood cells, 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)
- Breathing difficulty, chest pain, swelling of the face, fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver, redness of the skin
- 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
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon side effects (may affect up to 1 in 100 people) are:

- 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
- Enlarged lymph glands (sometimes painful), disorder of blood clotting system, failure of blood marrow, other blood cell changes (increased eosinophil and low white blood cells in blood)
- 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
- Problem with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, involuntary movement of the eye, 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
- Very fast heart rate or skipped heartbeats
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including widespread blistering rash and skin peeling, inflammation of the skin, the 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, 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
- Injection site reaction
- Life threatening allergic reaction

Rare side effects (may affect up to 1 in 1000 people) are:

- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Damage to the optic nerve resulting in vision impairment, clouding of the cornea
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Severe heart rhythm problems that may be life threatening

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

- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

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

As Voriconazole Fresenius Kabi has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

There have been reports of skin cancer in patients treated with Voriconazole Fresenius Kabi 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.

If any of these side effects persist or are troublesome, please tell your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.
[*For the printed material, please refer to the guidance of the annotated QRD template.]

5. How to store Voriconazole Fresenius Kabi

Unopened vial: This medicinal product does not require any special storage conditions.

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

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Voriconazole Fresenius Kabi contains

- The active substance is voriconazole.
- The other ingredients are hydroxypropylbetadex (MS 0.58-0.68), l-arginine, hydrochloric acid and sodium hydroxide.

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 Voriconazole Fresenius Kabi looks like and contents of the pack

Voriconazole Fresenius Kabi is presented in 25 ml single use glass vials as a white or almost white lyophilized powder for solution for infusion in pack sizes of 1 and 20 vials per carton.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

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

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

<[To be completed nationally]>

The following information is intended for healthcare professionals only:

Reconstitution and Dilution information

- Voriconazole Fresenius Kabi needs to first be reconstituted with either 19 ml of Water for Injections or 19 ml of 9 mg/ml (0.9 %) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml voriconazole.
- Discard the Voriconazole Fresenius Kabi vial if the vacuum does not pull the diluent into the vial.
- It is recommended to use a standard 20 ml (non-automated) syringe to ensure that the exact amount (19.0 ml) of Water for Injections or of 9 mg/ml (0.9 %) Sodium Chloride for Infusion is dispensed.
- The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final Voriconazole Fresenius Kabi solution containing 0.5 to 5 mg/ml of voriconazole.
- This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.
- Not for administration as a bolus injection.
- For storage information, please refer to Section 5 ‘How to store Voriconazole Fresenius Kabi’.

Required Volumes of 10 mg/ml Voriconazole Fresenius Kabi Concentrate

Body Weight (kg)	**Volume of Voriconazole Fresenius Kabi Concentrate (10 mg/ml) required for:**				
	3 mg/kg dose (number of vials)	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**	**8 mg/kg dose (number of vials)**	**9 mg/kg dose (number of vials)**
10	-	4.0 ml (1)	-	8.0 ml (1)	9.0 ml (1)
15	-	6.0 ml (1)	-	12.0 ml (1)	13.5 ml (1)
20	-	8.0 ml (1)	-	16.0 ml (1)	18.0 ml (1)
25	-	10.0 ml (1)	-	20.0 ml (1)	22.5 ml (2)
30	9.0 ml (1)	12.0 ml (1)	18.0 ml (1)	24.0 ml (2)	27.0 ml (2)
35	10.5 ml (1)	14.0 ml (1)	21.0 ml (2)	28.0 ml (2)	31.5 ml (2)
40	12.0 ml (1)	16.0 ml (1)	24.0 ml (2)	32.0 ml (2)	36.0 ml (2)
45	13.5 ml (1)	18.0 ml (1)	27.0 ml (2)	36.0 ml (2)	40.5 ml (3)
50	15.0 ml (1)	20.0 ml (1)	30.0 ml (2)	40.0 ml (2)	45.0 ml (3)
55	16.5 ml (1)	22.0 ml (2)	33.0 ml (2)	44.0 ml (3)	49.5 ml (3)
60	18.0 ml (1)	24.0 ml (2)	36.0 ml (2)	48.0 ml (3)	54.0 ml (3)
65	19.5 ml (1)	26.0 ml (2)	39.0 ml (2)	52.0 ml (3)	58.5 ml (3)
70	21.0 ml (2)	28.0 ml (2)	42.0 ml (3)	-	-
75	22.5 ml (2)	30.0 ml (2)	45.0 ml (3)	-	-
80	24.0 ml (2)	32.0 ml (2)	48.0 ml (3)	-	-
85	25.5 ml (2)	34.0 ml (2)	51.0 ml (3)	-	-
90	27.0 ml (2)	36.0 ml (2)	54.0 ml (3)	-	-
95	28.5 ml (2)	38.0 ml (2)	57.0 ml (3)	-	-
100	30.0 ml (2)	40.0 ml (2)	60.0 ml (3)	-	-

Voriconazole Fresenius Kabi is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted or diluted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (in a refrigerator), unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

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

Chemical and physical in-use stability of the diluted product has been demonstrated for 7 days at 2 °C to 8 °C.

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

Sodium Chloride 9 mg/ml (0.9 %) Solution for Injection
Compound Sodium Lactate Intravenous Infusion
5 % Glucose Intravenous Infusion
0.45 % Sodium Chloride Intravenous Infusion

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

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

Infusions of blood products must not occur simultaneously with Voriconazole Fresenius Kabi.

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

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