Virozole®

Voriconazole

1.Name of the medicinal product
Virozole® 200: film coated tablets; Box of 30.
2.Qualitative and quantitative composition
Virozole® 200: Each film coated tablet contains voriconazole 200 mg.
Excipient with known effect
Each tablet contains 288.00 mg lactose monohydrate.
For the full list of excipients, see section 6.1.
3.Pharmaceutical form
Film coated tablet.
4.Clinical particulars
4.1 Therapeutic indications
Virozole® is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:
-Treatment of invasive aspergillosis.
-Treatment of candidaemia in non-neutropenic patients.
-Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
-Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.
Virozole® should be administered primarily to patients with progressive, possibly life-threatening infections.
Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.
4.2 Posology and method of administration
Posology
Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.
Treatment
Adults
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral Voriconazole to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated.
Detailed information on dosage recommendations is provided in the following table:

	Intravenous	Oral	
		Patients 40 Kg and above*	Patients less than 40 Kg*
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg every 12 hours	200 mg every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

**This also applies to patients aged 15 years and older.*
Duration of treatment
Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance.
Dosage adjustment (Adults)
If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.
If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.
In case of use as prophylaxis, refer below.
Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg): Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.
The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading dose regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. It should be noted that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.
These oral dose recommendations for children are based on studies in which voriconazole was administered as the powder for oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a pediatric population. Considering the assumed limited gastro-enteric transit time in pediatric patients, the absorption of tablets may be different in pediatric compared to adult patients. It is therefore recommended to use the oral suspension formulation in children aged 2 to <12.
All other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight):
Voriconazole should be dosed as adults.
Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])
If patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). If patient is unable to tolerate treatment, reduce the dose by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially).
Use in pediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied.
Prophylaxis in Adults and Children
Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD).
Dosage
The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups. Please refer to the treatment tables above.
Duration of prophylaxis
The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.
Use of voriconazole in prophylaxis for greater than 180 days (6 months) requires careful assessment of the benefit-risk balance.
The following instructions apply to both Treatment and Prophylaxis
Dosage adjustment
For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered.
Dosage adjustments in case of co-administration
Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg).
The combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg).
Rifabutin or phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously twice daily.
Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.
Elderly
No dose adjustment is necessary for elderly patients.
Renal impairment
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment.
Voriconazole is hemodialysis with a clearance of 121 ml/min. A 4- hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.
Hepatic impairment
It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.
Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).
There is limited data on the safety of voriconazole in patients with abnormal Liver Function Tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).
Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with severe hepatic impairment must be carefully monitored for drug toxicity.
Pediatric population
The safety and efficacy of voriconazole in children below 2 years has not been established.
Method of administration
Virozole® film-coated tablets are to be taken at least one hour before, or one hour following, a meal.
4.3 Contraindications
-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
-Coadministration with CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.
-Coadministration with rifampicin, carbamazepine and phenobarbital since these medicinal products are likely to decrease plasma voriconazole concentrations significantly.
-Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations.
-Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose.
-Coadministration with ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, since increased plasma concentrations of these medicinal products can lead to ergotism.
-Coadministration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly.
-Coadministration with St. John's Wort.
4.4 Special warnings and precautions for use
Hypersensitivity
Caution should be used in prescribing Virozole® to patients with hypersensitivity to other azoles.
Cardiovascular
Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:
• Congenital or acquired QTc-prolongation.
• Cardiomyopathy, in particular when heart failure is present.
• Sinus bradycardia.
• Existing symptomatic arrhythmias.
•Concomitant medicinal product that is known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically-relevant threshold of 500 msec.
Monitoring of hepatic function
Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.
If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk- benefit of the treatment for the patient justifies continued use.
Monitoring of hepatic function should be carried out in both children and adults.
Visual adverse reactions
There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema.
Monitoring of renal function
Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.
Monitoring of pancreatic function
Patients, especially children, with risk factors for acute pancreatitis (e.g. recent chemotherapy, haematopoietic stem cell transplantation (HSCT)), should be monitored closely during voriconazole treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.
Dermatological adverse reactions
Patients have developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If a patient develops a rash, they should be monitored closely and voriconazole discontinued if lesions progress.
In addition voriconazole has been associated with phototoxicity, including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
Long-term treatment
Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and physicians should therefore consider the need to limit the exposure to voriconazole. The following severe adverse events have been reported in relation with long-term voriconazole treatment.
Squamous cell carcinoma of the skin (SCC) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.
Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis voriconazole discontinuation should be considered after multidisciplinary advice.
Pediatric population
Safety and effectiveness in pediatric subjects below the age of two years has not been established. Voriconazole is indicated for pediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the pediatric population. Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in pediatric patients aged 2 to <12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.
The frequency of phototoxicity reactions is higher in the pediatric population. As an evolution towards SCC has been reported, stringent measures for the photoprotection are warranted in this population of patients. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.
Prophylaxis
In case of treatment-related adverse events (hepatotoxicity, severe skin reactions including phototoxicity and SCC, severe or prolonged visual disorders and periostitis), discontinuation of voriconazole and use of alternative antifungal agents must be considered.
4.5 Interaction with other medicinal products and other forms of interaction
Voriconazole is metabolized by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolized by these CYP450 isoenzymes.
Unless otherwise specified, drug interaction studies have been performed in healthy adult male subjects using multiple dosing to steady state with oral voriconazole at 200 mg twice daily (BID). These results are relevant to other populations and routes of administration.
Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolized by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide), co-administration is contraindicated.
Interactions between voriconazole and other medicinal products are listed below:
- Astemizole, cisapride, pimozide, quinidine and terfenadine [CYP3A4 substrates]: Contraindicated.
- Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) [potent CYP450 inducers]: Contraindicated.
- Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate], Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID, Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID: Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated.
Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD.
When voriconazole treatment is stopped, the initial dose of efavirenz should be restored.
- Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]: Contraindicated.
- Rifabutin [potent CYP450 inducer] 300 mg QD, 300 mg QD (co-administered with

voriconazole 350 mg BID), 300 mg QD (co-administered with voriconazole 400 mg BID): Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk.
The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg).
Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.
- Rifampicin (600 mg QD) [potent CYP450 inducer]: Contraindicated.
- Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate] High dose (400 mg BID), Low dose (100 mg BID): Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated; Co-administration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
- St. John's Wort [CYP450 inducer; P-gp inducer] 300 mg TID (coadministered with voriconazole 400 mg single dose): Contraindicated
- Everolimus [CYP3A4 substrate, P-gP substrate]: Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations.
-Fluconazole (200 mg QD) [CYP2C9, CYP2C19 and CYP3A4 inhibitor]: The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
- Phenytoin [CYP2C9 substrate and potent CYP450 inducer] 300 mg QD, 300 mg QD (co-administered with voriconazole 400 mg BID): Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk.
Careful monitoring of phenytoin plasma levels is recommended.
Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID, (100 mg to 200 mg oral BID in patients less than 40 kg.
- Anticoagulants, Warfarin (30 mg single dose, co- administered with 300 mg BID voriconazole), [CYP2C9 substrate], Other oral coumarins (e.g., phenprocoumon, acenocoumarol) [CYP2C9 and CYP3A4 substrates]: Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
- Benzodiazepines (e.g., midazolam, triazolam, alprazolam) [CYP3A4 substrates]: Dose reduction of benzodiazepines should be considered.
- Immunosuppressants [CYP3A4 substrates], Sirolimus (2 mg single dose), Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy), Tacrolimus (0.1 mg/kg single dose): Coadministration of voriconazole and sirolimus is contraindicated. When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary. When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
- Long-Acting Opiates [CYP3A4 substrates], Oxycodone (10 mg single dose): Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.
- Methadone (32-100 mg QD) [CYP3A4 substrate]: Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [CYP2C9 substrates], Ibuprofen (400 mg single dose), Diclofenac (50 mg single dose): Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
- Omeprazole (40 mg QD) [CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]: No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
- Oral Contraceptives [CYP3A4 substrate; CYP2C19 inhibitor], Norethisterone/ethinylestradiol (1 mg/0.035 mg QD): Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
- Short-acting Opiates [CYP3A4 substrates], Alfentanil (20 µg/kg single dose, with concomitant naloxone), Fentanyl (5 µg/kg single dose): Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.
- Statins (e.g., lovastatin) [CYP3A4 substrates]: Dose reduction of statins should be considered.
- Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) [CYP2C9 substrates]: Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
- Vinca Alkaloids (e.g., vincristine and vinblastine) [CYP3A4 substrates]: Dose reduction of vinca alkaloids should be considered.
- Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir) [CYP3A4 substrates and inhibitors]: Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
- Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine) [CYP3A4 substrates, inhibitors or CYP450 inducers]: Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
- Cimetidine (400 mg BID) [non-specific CYP450 inhibitor and increases gastric pH]; Digoxin (0.25 mg QD) [P-gp substrate]; Indinavir (800 mg TID) [CYP3A4 inhibitor and substrate]; Macrolide antibiotics, Erythromycin (1 g BID) [CYP3A4 inhibitor] and Azithromycin (500 mg QD); Mycophenolic acid (1 g single dose) [UDP-glucuronyl transferase substrate]; Prednisolone (60 mg single dose) [CYP3A4 substrate]; Ranitidine (150 mg BID) [increases gastric pH]: No dose adjustment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of voriconazole in pregnant women available.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Virozole® must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Women of child-bearing potential

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

Breast-feeding

The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with Virozole®.

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats.

4.7 Effects on ability to drive and use machines

Virozole® has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.
The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analyzed by age, race, or gender.
Frequency categories are expressed as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).
- *Infections and infestations:* sinusitis (common); pseudomembranous colitis (uncommon).
- *Neoplasms benign, malignant and unspecified (including cysts and polyps)*: squamous cell carcinoma (not known);
- *Blood and lymphatic system disorders: agranulocytosis, pancytopenia, thrombocytopenia, leukopenia, anaemia:* agranulocytosis, pancytopenia, thrombocytopenia, leukopenia, anaemia (common); bone marrow failure, lymphadenopathy, eosinophilia (uncommon); disseminated intravascular coagulation (rare).
- *Immune system disorders:* hypersensitivity (uncommon); anaphylactoid reaction (rare).
- *Endocrine disorders:* adrenal insufficiency, hypothyroidism (uncommon); hyperthyroidism (rare).
- *Metabolism and nutrition disorders:* oedema peripheral (very common); hypoglycaemia, hypokalaemia, hyponatraemia (common).
- *Psychiatric disorders:* depression, hallucination, anxiety, insomnia, agitation, confusional state (common).
- *Nervous system disorders:* headache (very common); convulsion, syncope, tremor, hypertonia, paraesthesia, somnolence, dizziness (common); brain oedema, encephalopathy, extrapyramidal disorder, neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia (uncommon); hepatic encephalopathy, Guillain-Barre syndrome, nystagmus (rare).
- *Eye disorders*: visual impairment (very common); retinal haemorrhage (common); optic nerve disorder, papilloedema, oculogyric crisis, diplopia, scleritis, blepharitis (uncommon); optic atrophy, corneal opacity (rare).
- *Ear and labyrinth disorders:* hypoacusis, vertigo, tinnitus (uncommon).
- *Cardiac disorders:* arrhythmia supraventricular, tachycardia, bradycardia (common); ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia (uncommon); torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm (rare).
- *Vascular disorders:* hypotension, phlebitis (common); thrombophlebitis, lymphangitis (uncommon).
- *Respiratory, thoracic and mediastinal disorders:* respiratory distress (very common); acute respiratory distress syndrome, pulmonary oedema (common).
- *Gastrointestinal disorders*: diarrhea, vomiting, abdominal pain, nausea (very common); cheilitis, dyspepsia, constipation, gingivitis (common); peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis (uncommon).
- *Hepatobiliary disorders:* liver function test abnormal (very common); jaundice, jaundice cholestatic, hepatitis (common); hepatic failure, hepatomegaly, cholecystitis, cholelithiasis (uncommon).
- *Skin and subcutaneous tissue disorders:* rash (very common); dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema (common); Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema (uncommon); toxic epidermal necrolysis, angioedema, actinic keratosis, pseudoporphyria erythema multiforme, psoriasis, drug eruption (rare); cutaneous lupus erythematosus, ephelides, lentigo (not known).
- *Musculoskeletal and connective tissue disorders:* back pain (common); arthritis (uncommon); periostitis (not known).
- *Renal and urinary disorders:* renal failure acute, haematuria (common); renal tubular necrosis, proteinuria, nephritis (uncommon).
- *General disorders and administration site conditions:* pyrexia (very common); chest pain, face oedema, asthenia, chills (common); infusion site reaction, influenza like illness (uncommon).
- *Investigations:* blood creatinine increased (common); blood urea increased, blood cholesterol increased (uncommon).

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in pediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse reaction of photophobia of 10 minutes duration was reported.
There is no known antidote to voriconazole.
Voriconazole is hemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is hemodialysed with a clearance of 55 ml/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02 AC03

Mode of action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

5.2 Pharmacokinetic properties

Absorption

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC are reduced by 34% and 24%, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%. Cerebrospinal fluid samples from eight patients in a compassionate program showed detectable voriconazole concentrations in all patients.

Biotransformation

In vitro studies showed that voriconazole is metabolized by the hepatic cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4.
The inter-individual variability of voriconazole pharmacokinetics is high.
In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have on average 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.
The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.

Elimination

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.
After administration of a radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (> 94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.
The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200 mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate, povidone, starch, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Keep in original pack in intact conditions.

Date of revision

April, 2017

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.,
Dbayeh-Lebanon