SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VORİKANDİN 200 mg powder for solution for I.V. infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance :

Voriconazole 200 mg

Excipients:

Sulfobutyl ether beta cyclodextrin sodium……..3200 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VORIKONDIN is a powder for solution for infusion.

White lyophilized powder equivalent to 200 mg voriconazole in 30 ml transparent glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VORİKANDİN is a broad-spectrum, triazole antifungal agent and is indicated in the following fungal infections:

Treatment of invasive aspergillosis,

Treatment of candidaemia in non-neutropenic patients,

In the treatment of severe *Candida* infections, including *C. krusei* and esophageal and systemic *Candida* infections (hepatosplenic candidiasis, diffuse candidiasis, diffuse candidiasis).

Treatment of serious fungal infections caused by *Scedosporium* spp. *(S. apiospermum and S. prolificans)* and *Fusarium* spp.

In the treatment of other serious fungal infections in patients who cannot tolerate other treatments or who do not respond to treatment (*Aspergillus* species, *C. albicans*, non-Albicans species [*C. krusei* and *C. glabrata*], *S. apiospermum*, *S. prolificans* and *Fusarium species*).

In order to isolate and identify the organism causing the disease, samples for fungal culture should be provided and other relevant laboratory studies (serology, histopathology) should be

performed. Treatment can be started before the results of culture and other laboratory studies are obtained, but antifungal therapy should be adjusted as soon as the results are available.

4.2 Posology and method of administration

Posology:

It is recommended that VORİKANDİN I.V. is administered at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

It is not for bolus injection. It should be diluted for IV infusion.

Frequency and duration of administration

Adults

Treatment with VORİKANDİN must be initiated with the specified loading dose regimen given by either intravenous or oral route to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%; see section 5.2 Pharmacokinetic properties), switching between intravenous and oral administration is appropriate when clinically indicated.

Detailed information on dosage recommendations is provided in the following table:

	Intravenous	**Oral[a] (tablet and suspension)**	
		Patients 40 kg and above	**Patients less than 40 kg***
Loading dose regimen For all indications (first 24 hours)	6 mg/kg every 12 hours	400 mg every 12 hours (10 ml)	200 mg every 12 hours (5 ml)
Maintenance dose (after first 24 hours)			
Severe invasive *Candida*/Invasive aspergillosis/ *Scedosporium* and *Fusarium* infections/Other serious fungal infections[b]	4mg/kg every 12 hours	200 mg every 12 hours (5 ml)	100 mg every 12 hours (2.5 ml)
Candidaemia in non-neutropenic patients	3-4 mg/kg every 12 hours[c]	200 mg every 12 hours (5 ml)	100 mg every 12 hours (2.5 ml)
Esophageal Candida		200 mg every 12	100 mg every 12

infections	Not evaluated	hours (5 ml)	hours (2.5 ml)

* This also applies to patients aged 15 years and older.

a. In studies performed in healthy volunteers, an oral dose of 200 mg given every 12 hours provided a similar exposure (EAAτ) with a dose of 3 mg / kg IV given every 12 hours. An oral dose of 300 mg given every 12 hours provided a similar exposure (EAAτ) with a dose of 4 mg / kg IV given every 12 hours. (see Section 5.2)

b. Median duration of IV voriconazole therapy was 10 days (range 2-85 days) in a pivotal clinical study of invasive aspergillosis. Median duration of oral voriconazole therapy was 76 days (range 2-232 days) (See Section 5.1)

c. In clinical studies, patients with candidemia received 3 mg/kg every 12 hours as primary therapy, while patients with other deep tissue Candida infections received 4 mg/kg of salvage therapy. The appropriate dose should be determined by the nature and severity of the infection.

Dose adjustment

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.

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.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously every 12 hours (see sections 4.4 Special warnings and precautions for use and 4.5. Interaction with other medicinal products and other forms of interaction).

Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use should be avoided unless the benefit outweighs the risk

When voriconazole is coadministered with efavirenz the dose of voriconazole should be increased to 400 mg twice daily and the dose of efavirenz should be decreased by 50%, i.e. to 300 mg (once daily). When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored. (see sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

Treatment duration should be as short as possible depending on the patient's clinical and microbiological response.

The duration of treatment with the intravenous formulation should be no longer than 6 months (see section 5.3 Preclinical safety data). Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance. (see sections 4.4 Special warnings and precautions for use (Dermatological Reactions and 5.1 Pharmacodynamic properties (Duration of treatment)).

Method of administration

VORİKANDİN requires reconstitution and dilution (see section 6.6 Special precautions for disposal and other handling) prior to administration as an intravenous infusion.

VORİKANDİN solution for infusion is not recommended for bolus injection.

Additional information on special populations

Renal failure

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, sulfobutyl ether beta cyclodextrin sodium (SBECD), occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk-benefit to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see section 5.2 Pharmacokinetic properties).

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment. Based on conservative calculations (1st degree hemodialysis and minimal hepatic elimination), a 12-hour hemodialysis removes about 50% of the voriconazole from the body, while a 24-hour hemodialysis removes 75%.

The intravenous solvent SBECD is haemodialysed with a clearance of 55 ml/min.

Hepatic failure

It is recommended that the standard loading dose regimen of variconazole be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) (see section 5.2 Pharmacokinetic properties).

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 (see section 4.8 Undesirable effects).

Pediatric population

The recommended dosing regimen for maintenance in children aged 2 to <12 years and in young adolescents aged 12 to 14 years (< 50 kg) is as follows:

Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.

	Intravenous	**Oral**
Loading dose (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)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

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 dosage recommendations for children are based on studies of voriconazole in powder form for oral suspension. The bioequivalence between the tablet and the powder for oral suspension has not been investigated in pediatric population. Given the limited gastro-enteric transit time predicted in the pediatric population, the absorption of the tablets may be different compared to the adults. Therefore, it is recommended to use the oral suspension form in pediatric patients aged 2 to 12 years.

The safety and efficacy of Voriconazole in children below 2 years has not been established (See Section 4.8 Undesirable effects, 5.1 Pharmacodynamic properties) Voriconazole is therefore not recommended in children under the age of 2 years. Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see Section 4.8 Undesirable effects and 5.2 Pharmacokinetic properties).

Adult dose is used in all other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight)

Dose adjustment

If patient response to treatment is inadequate, the intravenous dose may be increased by 1 mg/kg steps.

If patient is unable to tolerate treatment, reduce the intravenous dose by 1 mg/kg steps.

Geriatric population

No dose adjustment is necessary for elderly patients (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to voriconazole or any of the excipients of VORİKANDİN.

It is contraindicated in children under 2 ages.

Coadministration of voriconazole with CYP3 A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration with sirolimus is contraindicated since voriconazole is likely to increase plasma concentrations of sirolimus significantly (See Section 4.5 Interaction with other medicinal products and other forms of interaction)

Coadministration with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration with rifabutin is contraindicated since this medicinal product is likely to decrease plasma voriconazole concentrations significantly (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk

Coadministration with ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates is contraindicated, since increased plasma concentrations of these medicinal products can lead to ergotism (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration with St. John's Wort is contraindicated (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Coadministration with high-dose ritonavir (400 mg and above twice daily) is contraindicated. Ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose. (see section 4.5, for lower doses see section 4.4).

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated. Efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity

Caution should be used in prescribing VORİKANDİN to patients with hypersensitivity to other azoles (see also section 4.8 undesirable effects).

Duration of treatment:

The duration of treatment with the intravenous formulation should be no longer than 6 months (see section 5.3 Preclinical safety data).

Cardiovascular undesirable effects

Voriconazole has been associated with QT interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole during clinical development and in post-marketing studies. These were cases who had multiple complicated 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 (see section 4.2 Posology and method of administration), 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 Posology and method of administration). 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. (See section 5.1 Pharmacodynamic properties)

Infusion-related reactions

Primarily flushing and nausea have been observed during administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment (see section 4.8 Undesirable effects).

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy.

Monitoring of hepatic functions

Patients receiving VORİKANDİN must be carefully monitored for hepatic toxicity. Laboratory evaluation of hepatic function (specifically AST and ALT) should be made at the initiation of treatment with VORİKANDİN and at least weekly for the first month of treatment. Treatment duration should be as short as possible, however, when the benefit of treatment outweighs the risk, the treatment should be continued. In such cases, monitoring can be monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, VORİKANDİN 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.

Severe dermatological reactions

- Phototoxicity:

In addition, VORİKANDİN has been associated with phototoxicity, including freckling, lentigo, actinic keratosis and pseudoporphyria. During VORİKANDİN treatment, all patients, including children, are advised to avoid exposure to direct sunlight and, when appropriate, use protective sunscreen / lotion or sunscreen.

- Squamous cell carcinoma (SCC):

Skin squamous cell carcinoma (SCC) has been reported in patients, including some patients who have had phototoxicity reactions. In case of phototoxic reactions, discontinuation of treatment with VORİKANDİN should be evaluated as multidisciplinary and the patient should be referred to the dermatologist. It should be considered to discontinue Voricon therapy and use an alternative antifungal agent. If VORİKANDİN treatment is continued despite the formation of lesions related to phototoxicity, dermatological evaluation should be done systemically and regularly to enable early diagnosis and to manage premalignant lesions. If a patient develops squamous cell carcinoma or premalignant skin lesions, VORİKANDİN treatment should be discontinued (See section "Long-term use" below.

- Exfoliative dermatitis reactions:

Patients have developed severe skin-threatening or fatal skin reactions during treatment with VORİKANDİN, such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction accompanied by eosinophilia and systemic symptoms (DRESS). If a rash develops in patients, the patient should be closely monitored, and if the lesions progress, VORİKANDİN should be stopped.

Long-term use:

More than 180 days (6 months) of use (treatment or prophylaxis) requires careful evaluation in terms of risk-benefit balance. The physician should consider whether or not VORİKANDİN treatment should be restricted (see section 4.2 and section 5.1 - duration of treatment). Regarding the long-term use of VORİKANDİN treatment, the following adverse reactions have been reported:

Squamous cell carcinoma (SCC) associated with long-term VORİKANDİN treatment has been reported.

In patients with organ transplantation, the periosteum that has not been caused by infection has been reported with elevated fluoride and alkaline phosphatase levels. If the patient has radiological findings that support a skeletal pain and periostitis, voriconazole therapy should be stopped after multidisciplinary evaluation.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema. (See section 4.8 Undesirable effects)

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products and have concurrent conditions that may result in decreased renal function (see section 4.8 Undesirable effects).

As cyclodextrin, an excipient of intravenous VORİKANDİN, is mainly excreted from the kidneys, oral therapy is recommended for patients with serum creatinine ≥ 220 micromol / L (2.5 mg / dL).

If oral treatment is not possible and the benefit is greater than risk, intravenous administration of VORİKANDİNE may be considered.

Monitoring of renal function

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine (See section 4.2 Posology and method of administration).

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 treatment with VORİKANDİN. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Dermatological adverse reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If a patient develops a rash he should be monitored closely and VORİKANDİN 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 treatment with VORİKANDİN and use measures such as protective clothing and sunscreen with high sun protection factor.

Long-term treatment

Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance. Physicians should therefore consider the need to limit the exposure to VORİKANDİN (see sections 4.2 Posology and method of administration and 5.1 Pharmacodynamic properties - Duration of treatment). The following severe adverse events have been reported in relation with long-term voriconazole treatment:

Squamous cell carcinoma of the skin (SCC):

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 for the discontinuation of VORİKANDİN and the patient should be referred to a dermatologist. VORİKANDİN discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever VORİKANDİN is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. VORİKANDİN should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

Side effects related to skeletal system

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.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). Voriconazole is indicated for paediatric patients aged two years or older. A higher frequency

of liver enzyme elevations was observed in the paediatric population (see section 4.8). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2 to < 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

Serious dermatological reactions (including SCC)

The frequency of phototoxicity reactions is higher in the paediatric 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.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole is coadministered with efavirenz the dose of voriconazole should be increased to 400 mg every 12 hours and the dose of efavirenz should be decreased to 300 mg every 24 hours (see sections 4.2 Posology and method of administration; see Section 4.5 Interaction with other medicinal products and other forms of interaction for standard doses of efavirenz and voriconazole).

Rifabutin (Potent CYP450 inducer)

Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Ritonavir (Potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see sections 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.3 Contraindications).

Everolimus (CYP3A4 substrate, P-gp substrate)

Coadministration of voriconazole with everolimus is not recommended. Because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation. (See section 4.5)

Methadone (CYP3A4 substrate)

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following coadministration of voriconazole. Dose reduction of methadone may be needed (See Section 4.5 Interaction with other medicinal products and other forms of interaction).

Short acting opiates (CYP3A4 substrate)

Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil) should be considered when coadministered with voriconazole (see section 4.5 Interaction with other medicinal products and other forms of interaction). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl frequent monitoring for opiate-associated adverse reactions (including a longer respiratory monitoring period) may be necessary.

Long acting opiates (CYP3A4 substrate)

Reduction in the dose of oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC of voriconazole in healthy subjects. 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. (See section 4.5)

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.

4.5 Interaction with other medicinal products and other forms of interaction

Voriconazole is metabolised 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 metabolised 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 metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) coadministration is contraindicated (see below and section 4.3).

Interaction table

Interactions between voriconazole and other medicinal products are listed in the table below (once daily as "QD", twice daily as "BID", three times daily as "TID" and not determined as "ND"). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range. The asterisk (*) indicates a two-way interaction. AUC, AUC_t and $AUC_{0-\infty}$ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

The interactions in the table are presented in the following order: contraindications, those requiring dose adjustment and careful clinical and/or biological monitoring, and finally those that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field.

Medicinal product *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Astemizole, cisapride, pimozide, quinidine and terfenadine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated** (See section 4.3)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated** (See section 4.3)
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*	 Efavirenz C_{max} ↑ 38% Efavirenz AUCτ ↑ 44% Vorikonazol C_{max} ↓ 61% Voriconazole AUCτ ↓ 77% Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUCτ ↓ 7%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see section 4.3). 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 (see section 4.2 and 4.4).
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	**Contraindicated** (See section 4.3)

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Rifabutin *[potent CYP450 inducers]* 300 mg QD 300 mg QD (coadministered with voriconazole 350 mg BID)* 300 mg QD (coadministered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 69% Voriconazole AUCτ ↓ 78% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUCτ ↓ 32% Rifabutin C_{max} ↑ 195% Rifabutin AUCτ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 104%	**Contraindicated** (See section 4.3) 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

	Voriconazole AUCτ ↓ 87%	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]*	Voriconazole C_{max} ↓ 93% Voriconazole AUCτ ↓ 96%	**Contraindicated** (See section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUC ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUCτ ↓ 82% Ritonavir C_{max} ↓ 25% Ritonavir AUCτ ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUCτ ↓ 39%	Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see section 4.3). Coadministration 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.
Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
St John's Wort *[CYP450 inducers; P-gp inducer]* 300 mg TID (coadministered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%	**Contraindicated** (See section 4.3)
Everolimus *[CYP3A4 substrate, P-gP substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase

		everolimus concentrations (see section 4.4).
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57% Voriconazole AUCτ ↑ 79% Fluconazole C_{max} ND Fluconazole AUCτ ND	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 strong CYP450 inducer]* 300 mg QD 300 mg QD (coadministered with voriconazole 400 mg BID)*	Voriconazole C_{max} ↓ 49% Voriconazole AUCτ ↓ 69% Phenytoin C_{max} ↑ 67% Phenytoin AUCτ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUCτ ↑ 39%	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 coadministered 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) (see section 4.2).

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Anticoagulants Warfarin (30 mg single	Maximum increase in	Close monitoring of

dose, co- administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (e.g., phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	prothrombin time was approximately 2-fold Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	prothrombin time or other suitable anticoagulation tests is recommended. The dose of anticoagulants should be adjusted accordingly.
Benzodiazepines (e.g., midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	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)	 In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold Ciclosporin C_{max} ↑ 13% Ciclosporin AUCτ ↑ 70%	 Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3). 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. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u>

Medicinal product *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUCτ ↑ 221%	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)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	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]*	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUCτ ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUCτ ↑ 103%	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	S-Ibuprofen C_{max} ↑ 20%	Frequent monitoring for adverse reactions and toxicity related to

dose) Diclofenac (50 mg single dose)	S-Ibuprofen $AUC_{0-\infty}$ ↑ 100% Diclofenac C_{max} ↑ 114% Diclofenac $AUC_{0-\infty}$ ↑ 78%	NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

Medicinal product *[Mechanism of interaction]*	**Interaction Geometric mean changes (%)**	**Recommendations concerning coadministration**
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116% Omeprazole AUCτ ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUCτ ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	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)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUCτ ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUCτ ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUCτ ↑ 46%	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)	 In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study,	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

	Fentanyl $AUC_{0-\infty}$ ↑ 1.34-fold	other opiate-associated adverse reactions is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	Dose reduction of statins should be considered.
Sulphonylureas (e.g., tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.

Medicinal product ***[Mechanism of interaction]***	**Interaction Geometric mean changes (%)**	**Recommendations concerning coadministration**
Vinca Alkaloids (e.g., vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. In vitro studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease 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*	Not studied clinically. In vitro studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.

inducers]	The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18% Voriconazole AUCτ ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) *P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment
Indinavir (800 mg QD) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUCτ ↔ Voriconazole C_{max} ↔ Voriconazole AUCτ ↔	No dose adjustment

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	 Voriconazole C_{max} and AUCτ ↔ Voriconazole C_{max} and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	 No dose adjustment
Mycophenolic acid (1 g single dose) *UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: D.

Women with childbearing potential/Contraception:

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

Pregnancy

Voriconazole has harmful pharmacological effects on pregnancy and / or fetus / newborn. VORİKANDİN must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Lactation

It is not known whether voriconazole is excreted in human milk. Breast-feeding must be stopped on initiation of treatment with voriconazole.

Reproduction ability/Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats. (See Section 5.3 Preclinical safety data). Potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

VORİKANDİN may have an impact on the ability to drive and use machines.

Voriconazole 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.

Patients are advised not to drive at night, especially when using voriconazole.

4.8 Undesirable effects

The safety profile of voriconazole is based on an integrated safety database of more than 2,000 subjects (including 1,603 patients in therapeutic trials and 270 adults in prophylaxis trials). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers.

The most commonly reported adverse reactions were visual disturbances, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema 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 analysed by age, race, or gender.

In the table below, since the majority of the studies were of an open nature all causality adverse reactions and their frequency categories in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies, by system organ class and frequency, are listed.

Frequency categories are expressed as Very common (≥ 1/10); common (≥ 1/100 to< 1/10); uncommon (≥ 1/1000 to< 1/100); rare (≥ 1/10000 to< 1/1000); very rare (< 1/10000) and unknown (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are shown order of decreasing seriousness.

Infections and Infestations

Common : Sinusitis

Uncommon : Pseudomembranous colitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Unknown : Squamous cell carcinoma (SCC)*

Blood and lymphatic system disorders

Common : Agranulocytosis[1], pancytopenia, thrombocytopenia[2], leukopenia, anaemia

Uncommon : Bone marrow failure, lymphadenopathy, eosinophilia

Rare : Disseminated intravascular coagulation

Immune system disorders

Uncommon : Hypersensitivity
Rare : Anaphylactoid reaction

Endocrine disorders:

Uncommon : Adrenal insufficiency, hypothyroidism

Rare : Hyperthyroidism

Metabolism and nutrition disorders

Very common : Peripheral oedema

Common : Hypoglycaemia, hypokalaemia, hyponatraemia

Psychiatric disorders

Common : depression, hallucination, anxiety, insomnia, agitation, confusional state

Nervous system disorders

Very common : Headache

Common : convulsion, syncope, tremor, hypertonia[3], paraesthesia, somnolence, dizziness

Uncommon : brain oedema, encephalopathy[4], extrapyramidal disorder[5], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia

Rare : Hepatic encephalopathy, Guillain-Barre syndrome, nystagmus

Eye disorders

Very common : Visual impairment[6]

Common : Retinal haemorrhage

Uncommon : optic nerve disorder[7], papilloedema[8], oculogyric crisis, diplopia, scleritis, blepharitis

Rare : optic atrophy, corneal opacity

Ear and Labyrinth Disorders

Uncommon : Hypoacusis, vertigo, tinnitus

Cardiac disorders

Common : Arrhythmia supraventricular, tachycardia, bradycardia

Uncommon : ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia

Rare : Torsades de pointes, atrioventricular block complete, bundle branch lock, nodal rhythm

Vascular disorders

Common : Hypotension, phlebitis

Uncommon : Thrombophlebitis, lymphangitis

Respiratory, thoracic and mediastinal disorders

Very common : Respiratory distress[9]

Common : Acute respiratory distress syndrome, pulmonary oedema

Gastrointestinal disorders

Very common : Diarrhoea, vomiting, abdominal pain, nausea

Common : Cheilitis, dyspepsia, constipation, gingivitis

Uncommon : Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis

Hepatobiliary disorders

Very common : Liver function test abnormal

Common : Jaundice, jaundice cholestatic, hepatitis[10]

Uncommon : Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis

Skin and subcutaneous tissue disorders:

Very common : Rash

Common : Dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema

Uncommon : Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema

Rare : Toxic epidermal necrolysis, eosinophilia and accompanying systemic symptoms drug reaction (DRESS)[8], angioedema, actinic keratosis*, pseudoporphyria erythema multiforme, psoriasis, drug eruption

Unknown : Cutaneous lupus erythematosus*, ephelides*, lentigo*

Musculoskeletal and connective tissue disorders

Common : Back pain

Uncommon : Arthritis

Unknown : Periostitis*

Renal and urinary disorders

Common : Renal failure acute, hematuria

Uncommon : Renal tubular necrosis, proteinuria, nephritis

General disorders and administration site conditions

Very common : Pyrexia

Common : Chest pain, face oedema[11], asthenia, chills

Uncommon : Infusion site reaction, influenza like illness

Investigations:

Common : Blood creatinine increased

Uncommon: Blood urea increased, blood cholesterol increased

* These side effects are from post-marketing reports

1. Includes febrile neutropenia and neutropenia.

2. Includes immune thrombocytopenic purpura.
3. Includes nuchal rigidity and tetany.
4. Includes hypoxicischaemic encephalopathy and metabolic encephalopathy.
5. Includes akathisia and parkinsonism.
6. See “Visual impairments” paragraph in section 4.8.
7. Prolonged optic neuritis has been reported postmarketing. See section 4.4. See Section 4.4.
8. See Section 4.4.
Includes dyspnoea and dyspnoea exertional.
10. Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.
11. Includes periorbital oedema, lip oedema, and oedema mouth.

Description of selected adverse reactions

Visual impairments

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole.

There have been post-marketing reports of prolonged visual adverse events (see section 4.4 Special warnings and precautions for use).

Dermatological adverse reactions

Dermatological reactions were common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiform (rare) during treatment with voriconazole.

If a patient develops a rash they should be monitored closely and VORİKANDİN discontinued if lesions progress.

Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy.

There have been reports of squamous cell carcinoma of the skin in patients treated with voriconazole for long periods of time; the mechanism has not been established (see section 4.4 Special warnings and precautions for use).

Liver function tests

The overall incidence of transaminase increases >3 x ULN (not necessarily comprising an adverse event) in the voriconazole clinical programme was 18 % (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole for pooled therapeutic and prophylaxis. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death.

Infusion-related reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion (see section 4.4 Special warnings and precautions for use).

Paediatric population

The safety of voriconazole was investigated in 288 paediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105) in clinical trials. The safety of voriconazole was also investigated in 158 additional paediatric patients aged 2 to <12 years in compassionate use programs. Overall the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of liver enzyme elevations, reported as adverse

events in clinical trials was observed in paediatric patients as compared to adults (14.2% transaminases increased in paediatrics compared to 5.3% in adults). Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1).

There have been post-marketing reports of pancreatitis in paediatric patients.

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric 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, in case of overdose, symptomatic and supportive treatment is recommended.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55 ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole and the intravenous vehicle SBECD from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antimycotics for systemic use - Triazole derivatives

ATC Code: J02AC03

Mechanism 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.

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against Candida species (including fluconazole resistant C. *krusei* and resistant strains of C. *glabrata* and C. *albicans*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents.

Clinical efficacy defined as partial or complete response has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans*, Candida spp., including *C. albicans, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* and limited numbers of *C. dubliniensis, C. inconspicua*, and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum*, *S. prolificans* and *Fusarium* spp..

Other treated fungal infections (often with either partial or complete response) included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium* spp., *Coccidioides immitis, Conidiobolus coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomatis, Paecilomyces lilacinus, Penicillium spp. including P. marneffei, Phialophora richardsiae, Scopulariopsis brevicaulis* and *Trichosporon* spp. including *T. beigelii* infections.

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp. and *Histoplasma capsulatum*. Most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 µg/ml.

In vitro activity against the following pathogens has been shown, but the clinical significance is unknown: *Curvularia* spp. and *Sporothrix* spp.

Breakpoints
In order to isolate and identify the organism causing the disease, samples for fungal culture should be provided and other relevant laboratory studies (serology, histopathology) should be performed. Treatment can be started before the results of culture and other laboratory studies are obtained, but antifungal therapy should be adjusted as soon as the results are available.

The species most frequently involved in causing human infections include *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata* and *C. krusei*, all of which usually exhibit minimal inhibitory concentration (MICs) of less than 1 mg/L for voriconazole.

However, the *in vitro* activity of voriconazole against *Candida* species is not uniform. Specifically, for *C. glabrata*, the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates. Therefore, every attempt should be made to identify *Candida* to species level. If antifungal susceptibility testing is available, the MIC results may be interpreted using breakpoint criteria established by EUCAST (European Committee on Antimicrobial Susceptibility Testing).

EUCAST Breakpoints

Candida species	**MIC breakpoint (mg/L)**	
	≤S (Susceptible)	**>R (Resistant)**
Candida albicans[1]	0.125	0.125
Candida tropicalis[1]	0.125	0.125

Candida parapsilosis[1]	0.125	0.125
Candida glabrata[2]	Insufficient evidence	
Candida krusei[3]	Insufficient evidence	
Diğer Candida spp.[4]	Insufficient evidence	

[1]Strains with MIC values above the Susceptible (S) breakpoint are rare, or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.
[2]In clinical studies, response to voriconazole in patients with *C glabrata* infections was 21% lower compared to *C. albicans, C. parapsilosis* and *C. tropicalis*. However, there was no correlation between this decreased response and increased MIC values.
[3]In clinical studies, response to voriconazole in *C. krusei* infections was similar to *C. albicans, C. parapsilosis* and *C. tropicalis*. However, as there were only 9 cases available for EUCAST analysis, there is currently insufficient evidence to set clinical breakpoints for C. krusei.
[4]EUCAST has not determined non-species related breakpoints for voriconazole.

Clinical experience

Successful outcome in this section is defined as complete or partial response.

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis Voriconazole has in vitro fungicidal activity against Aspergillus spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53 % of voriconazole-treated patients compared to 31 % of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator.

This study confirmed findings from an earlier, prospectively designed study.

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients: The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia

was demonstrated in an open, comparative study. 377 non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and 5 in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medicinal product was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of Candida from blood and infected deep tissue sites 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this 12th week analysis following EOT a successful response was seen in 41 % of patients in both treatment arms.

In a secondary analysis, which utilised DRC assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65 % and 71 %, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

Time	Voriconazole (n=248)	Amphotericin B → fluconazole (N=122)
EOT	178 (72%)	88 (72%)
2 weeks after EOT	125 (50%)	62 (51%)
6 weeks after EOT	104 (42%)	55 (45%)
12 weeks after EOT	104 (42%)	51 (42%)

Serious refractory Candida infections:

The study comprised 55 patients with serious refractory systemic Candida infections (including candidaemia, disseminated and other invasive candidiasis) where prior antifungal treatment, particularly with fluconazole, had been ineffective. Successful response was seen in 24 patients (15 complete, 9 partial responses). In fluconazole-resistant non albicans species, a successful outcome was seen in 3/3 C. krusei (complete responses) and 6/8 C. glabrata (5 complete, 1 partial response) infections. The clinical efficacy data were supported by limited susceptibility data.

Scedosporium and Fusarium infections

Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with S. apiospermum and in 2 (both partial responses) of 7 patients with S. prolificans infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including Scedosporium spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. 4 additional patients with fusariosis had an infection caused by several organisms. 2 of them had a successful outcome.

The majority of patients receiving voriconazole treatment of the above mentioned rare infections were intolerant of, or refractory to, prior antifungal therapy.

Duration of treatment

In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

Experience in Paediatric population

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in 2 prospective, open-label, noncomparative, multicenter clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. For patients with IA the overall rates of global response at 6 weeks were 64.3% (9/14). The global response rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age. For patients with ICC the global response rate at EOT was 85.7% (6/7) and for patients with EC the global response rate at EOT was 70% (7/10). The overall rate of response (ICC and EC combined) was 88.9% (8/9) for 2 to <12 years old and 62.5% (5/8) for 12 to <18 years old.

Clinical studies examining QTc interval

A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QTc interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole were 5.1, 4.8, and 8.2 msec, respectively and 7.0 msec for ketoconazole 800 mg. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

5.3 Pharmacokinetic properties

General properties:

The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

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.

Increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2.5-fold increase in exposure (AUC). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV.
When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.
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 (CSF) samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

Biotransformation

In vitro studies showed that voriconazole is metabolised 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 metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5 %. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser 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.

Linearity/Non-linearity

During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose.

Special Populations

Gender

In an oral multiple dose study, Cmax and AUC for healthy young females were 83 % and 113 % higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in Cmax and AUC were observed between healthy elderly males and healthy elderly females (≥65 years).

In the clinical programme, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female patients were similar. Therefore, no dosage adjustment based on gender is necessary.

Elderly:

In an oral multiple dose study C_{max} and AUC in healthy elderly males (≥65 years) were 61 % and 86 % higher, respectively, than in healthy young males (18-45 years). No significant differences in C_{max} and AUC were observed between healthy elderly females (≥65 years) and healthy young females (18- 45 years).

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed however, the safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly.

Children:

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to <17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg, and 200 mg twice daily were evaluated in 3 paediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in paediatric patients compared to adults.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients. This is due to a greater liver mass to body mass ratio.

Oral bioavailability may, however, be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adolescents/adults. Based on the population pharmacokinetic analysis, 12- to 14- year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

Renal failure:

In patients with moderate to severe renal dysfunction (creatinine clearance concentration ≥2.5 mg/dL), accumulation of the intravenous vehicle, sulfobutyl ether beta cyclodextrin sodium (SBECD), occurs as it is mainly excreted in urine (See Section 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use).

Hepatic failure

After an oral single dose (200 mg), AUC was 233 % higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C).

Pharmacokinetic/ Pharmacodynamic relationship

In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425 ng/ml (inter-quartile range 1193 to 4380 ng/ml) and 3742 ng/ml (inter-quartile range 2027 to 6302 ng/ml), respectively.

A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

5.3 Preclinical safety data

Repeated-dose toxicity studies with voriconazole indicated the liver to be the target organ. Hepatotoxicity occurred at plasma exposures similar to those obtained at therapeutic doses in humans, in common with other antifungal agents. In rats, mice and dogs, voriconazole also induced minimal adrenal changes. Conventional studies of safety pharmacology, genotoxicity or carcinogenic potential did not reveal a special hazard for humans.

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre and post-natal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of oestradiol levels, and are consistent with those observed with other azole antifungal agents.

Preclinical data on the intravenous vehicle SBECD indicated that the main effects were vacuolation of urinary tract epithelium and activation of macrophages in the liver and lungs in the repeated-dose toxicity studies. As GPMT (guinea pig maximization test) result was

positive, prescribers should be aware of the hypersensitivity potential of the intravenous formulation. Standard genotoxicity and reproduction studies with the excipient SBECD reveal no special hazard for humans. Carcinogenicity studies were not performed with SBECD. An impurity present in SBECD has been shown to be an alkylating mutagenic agent with evidence for carcinogenicity in rodents. This impurity should be considered a substance with carcinogenic potential in humans. In light of these data the duration of treatment with the intravenous formulation should be no longer than 6 months.

6. PHARMACEUTICAL PROPERTIES

6.1 List of Excipients

Sulfobutyl ether beta cyclodextrin sodium (SBECD)

Water for injection

6.2 Incompatibilities

VORİKANDİN must not be infused into the same line or cannula concomitantly with other intravenous products. When the infusion is complete, the line may be used for administration of other intravenous products.

Blood products and short-term infusion of concentrated solutions of electrolytes:

Electrolyte disturbances such as hypokalemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of VORİKANDİN therapy (see sections 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use).

VORİKANDİN must not be administered simultaneously with any blood product or any short-term infusion of concentrated solutions of electrolytes, even if the two infusions are running in separate lines.

Total parenteral nutrition (TPN)

Total parenteral nutrition (TPN) need not be discontinued when prescribed with VORİKANDİN, but does need to be infused through a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for VORİKANDİN.

VORİKANDİN must not be diluted with 4.2% Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

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

The 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.

6.5 Nature and contents of container

Colorless Type I glass vial sealed with rubber stopper and flip-off cap.

6.6 Special precautions for disposal and other handling

VORİKANDİN 200 mg I.V. Powder for Solution for Infusion is available in single-use vials. The powder is 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 of 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. This product is for single use only, any unused solution should be discarded. Only clear colourless solutions without particles should be used.

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.

Required Volumes of 10 mg/ml VORİKANDİN Concentrate

Body weight (kg)	Volume of VORİKANDİN Concentrate (10mg/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 Powder for IV Solution for Infusion is a sterile single-dose vial 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 9 mg/ml (0.9%) Solution 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

The compatibility of VORİKANDİN with diluents other than described above or in section 6.2 is unknown.

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

7. MARKETING AUTHORISATION HOLDER

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