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Voriconazole
In the Treatment of Invasive Aspergillosis

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Contents

Abstract

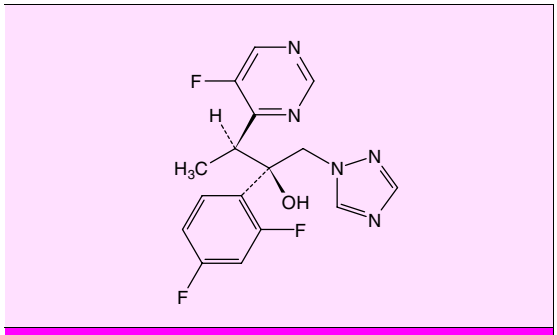
▲ Voriconazole, a broad-spectrum triazole antifungal agent, inhibits the cytochrome P450-dependent enzyme 14-α-sterol demethylase, thereby disrupting the fungal membrane and stopping fungal growth. The drug shows excellent *in vitro* activity against *Aspergillus* spp., including itraconazole- and amphotericin B-resistant *A. fumigatus* isolates.

▲ At 12 weeks, 52.8% of voriconazole recipients achieved a successful outcome (complete or partial response) versus 31.6% of amphotericin B recipients in a randomised, nonblind trial in 392 patients (aged ≥12 years) with invasive aspergillosis. Patients received intravenous voriconazole (6 mg/kg once every 12 hours on day 1, then 4 mg/kg once every 12 hours for ≥7 days; patients could then be switched to oral voriconazole 200mg once every 12 hours) or intravenous amphotericin B (1 to 1.5 mg/kg/day for ≥14 days). At the investigators' discretion, those who failed to respond to or experienced toxicity with the initial randomised drug could be switched to other licensed antifungal therapy.

▲ Voriconazole was generally well tolerated. The most common treatment-related adverse events were transient visual disturbances (≈30% of patients) and skin rashes (6%).

▲ Voriconazole was generally better tolerated than amphotericin B; voriconazole recipients experienced significantly ($p < 0.02$ both comparisons) fewer treatment-related adverse events or serious adverse events. The incidence of visual disturbances was significantly ($p < 0.001$) higher with voriconazole than amphotericin B treatment.

Features and properties of voriconazole (UK-109,496)	
Indications	
Treatment of invasive aspergillosis	
Mechanism of action	
Fungicidal	Cytochrome P450-dependent 14-α-sterol demethylase inhibitor
Dosage and administration	
Recommended dosage in adults	Intravenous loading regimen of 6 mg/kg once every 12h for 1 day, then 4 mg/kg once every 12h; patients may be switched to oral 100mg once every 12h in those weighing <40kg or a 200mg dosage in those ≥40kg
Route of administration	Intravenous or oral
Frequency of administration	Once every 12h
Pharmacokinetic profile (Steady state 6 mg/kg/day orally)	
Peak plasma concentration	2.4 mg/L
Time to peak plasma concentration	≤2 h
Area under the plasma concentration-time curve	11.17 mg • h/L
Bioavailability	96%
Elimination half-life	≈6h
Adverse events	
Most frequent	Transient visual disturbances, skin rash



Voriconazole

The number of patients infected with a variety of fungal pathogens has been steadily growing over the past two decades,[1] with *Aspergillus* and *Candida* species the most common fungal pathogens.[2] A key reason for this increase in the incidence of fungal infections, in particular aspergillosis, is the increasing and more intensive use of chemotherapy and the advent of allogenic bone marrow transplantation. Voriconazole is a new orally or intravenously administered broad-spectrum antifungal belonging to the triazole class of drugs, with activity against yeasts, moulds and dermatophytes.

This review focuses on the pharmacological properties and therapeutic use of voriconazole in the treatment of aspergillosis. Discussion of its activity against other yeasts, moulds or dermatophytes or the use of the drug in the treatment of other fungal infections is beyond the scope of this review.

1. Pharmacodynamic Profile

• Voriconazole is a derivative of fluconazole. Like other members of the triazole class, the drug inhibits the cytochrome P450 (CYP)-dependent enzyme 14-α-sterol demethylase, thereby preventing the conversion of lanosterol to ergosterol, which results in the accumulation of methylated sterols and depletion of ergosterol. This, in turn, disrupts the fungal membrane and halts fungal growth.[3]

• Voriconazole is a more effective inhibitor of 14-α-sterol demethylase than fluconazole.[3] Whereas voriconazole completely inhibited ergosterol synthesis in fluconazole-susceptible and -resistant strains of *Candida albicans*, fluconazole only partially inhibited synthesis (about 40% inhibition against both *C. albicans* strains). This may explain why voriconazole is active against moulds that show resistance to fluconazole, and possibly other azole antifungals.[3]

In Vitro Studies

A standardised method for susceptibility testing of various moulds *in vitro* is described in the National Committee for Clinical Laboratory Standards (NCCLS) M38P document.[4] It is important to stress, however, that minimum inhibitory concentrations (MICs) of antifungal agents vary between laboratories and do not necessarily correlate with clinical outcome.[5,6]

• Voriconazole demonstrates excellent activity against clinical isolates of *Aspergillus* spp. *in vitro*. Minimum concentrations of voriconazole required to inhibit 90% of isolates tested (MIC_{90}s) using assays based on the NCCLS-M38P recommendations were typically 0.25 to 1 mg/L.[7-11] Species tested were *A. fumigatus*, *A. flavus*, *A. niger* and, less commonly, *A. nidulans*.

• Ninety-eight percent of 239 *Aspergillus* spp. clinical isolates were susceptible *in vitro* to voriconazole at an MIC value of ≤1 mg/L in a SENTRY Surveillance Program study.[12] To date, the correlation between *in vitro* and *in vivo* activity has not been determined. Voriconazole showed similar activity to posaconazole (98% of isolates susceptible) and ravuconazole (92%), with all three agents being more active than amphotericin B (89%) or itraconazole (72%) against these isolates collected at 16 medical centres in the USA and Canada between January and December 2000.

• Notably, voriconazole showed marked activity against itraconazole- (n=28) or amphotericin B- (n=18) resistant *A. fumigatus* isolates (MIC range 0.25 to 2 mg/L) using a broth macrodilution

method (MIC defined as lowest drug concentration at which there was no visible growth).[13] No *in vitro* cross-resistance to itraconazole or amphotericin B was found for *A. fumigatus* in this study.[13]

• For amphotericin B-resistant *A. terreus* isolates (n=101) the 48-hour mean MIC for voriconazole was 0.22 mg/L.[14] MIC_{90}s for voriconazole and amphotericin B were similar or within two dilutions of each other against amphotericin B-sensitive *A. terreus*.[9]

Animal Studies

• Oral voriconazole showed good antifungal activity against *A. fumigatus* in an experimental rat model of invasive pulmonary aspergillosis.[15] Seven days after infection, the survival rate in voriconazole-treated animals (30 mg/kg once daily for 5 days) was significantly ($p < 0.02$) higher than that in the control group (100 vs 37.5%; n=8 per group). The survival rate (75% of animals) in the oral itraconazole group (30 mg/kg once daily for 5 days) was not significantly different from that in the corresponding control group (41.6%).[15]

• These data were confirmed in a guinea pig model of disseminated invasive aspergillosis caused by *A. fumigatus* infection[16] and in immunosuppressed, leucopenic rabbits[17] lethally infected with *A. fumigatus*. For example, in the guinea pig model, all animals treated with voriconazole 10 mg/kg twice daily survived, whereas no animals in the control group survived.[16] In addition, there were significant reductions in tissue colony counts of *A. fumigatus* in liver, lung, kidney and brain tissue of voriconazole-treated animals ($p < 0.003$ vs control).[16] Treatment started 24 hours after challenge and continued for 5 days.[16]

• Voriconazole was also highly effective in the prevention and treatment of experimental *A. fumigatus* endocarditis in guinea pigs.[18] All 12 animals infected with the pathogen were cured after 7 days' treatment with oral voriconazole 10 mg/kg twice daily. Moreover, initiating intraperitoneal voriconazole (10 mg/kg twice daily) 2 days before inoculation of the pathogen and continuing treatment for 3 days after inoculation, prevented endocarditis in all but 1 of the 12 animals. In contrast, itraconazole prophylaxis or therapeutic treatment was ineffective in this model of endocarditis, when given at the same dosages and by the same route of administration.[18]

2. Pharmacokinetic Profile

The pharmacokinetic properties of intravenous or oral voriconazole have been evaluated in healthy adult volunteers,[19-22] in adults[22] and children[22,23] with fungal infections, in patients with chronic mild to moderate (Child Pugh class A or B) hepatic impairment,[22] in those with mild to severe renal impairment[22] and in *in vitro*[22] studies. Some of these data have been obtained from the manufacturer's prescribing information.[22]

Absorption and Distribution

• Voriconazole is rapidly absorbed after oral administration; maximum serum concentrations (C_{max}) were reached in ≤2 hours.[21,24] The oral bioavailability of voriconazole is estimated to be 96% based on pooled data from 207 healthy volunteers.[20-22]

• In two studies in healthy adult volunteers, voriconazole showed nonlinear kinetics, with marked interindividual variability in C_{max} and the area under the plasma concentration-time curve (AUC).[19,24] However, there was little intraindividual variability in C_{max} values.[22] On average, oral voriconazole reached steady-state plasma concentrations after 3 to 5 days in healthy male volunteers receiving 4 mg/kg once daily, 2 or 3 mg/kg twice daily, or 1.5 or 2 mg/kg three times daily.[24] Mean C_{max} values were 2.1, 1.0, 2.4, 1.1 and 2.2 mg/L, respectively, for each of these dosage regimens (8 to 11 volunteers per group).[24] Corresponding mean AUC within a dose administration interval (AUC_τ) values were 13.19, 4.30, 11.17, 3.79 and 9.04 mg • h/L.[24] As predicted, mean C_{max} values were higher after intravenous than oral administration, although trough concen-

trations exceeded the MIC for *Aspergillus* spp. after both intravenous or oral administration.[19]

• Systemic exposure to voriconazole was reduced in the fed state compared with that in the fasted state.[22] Mean C_{max} and AUC_{τ} values were reduced by 34 and 24% in healthy volunteers fed a high fat meal.[22]

• Minimum plasma concentrations at steady state were >0.8 mg/L after intravenous voriconazole 3 mg/kg once every 12 hours in 12 healthy volunteers.[25] The mean steady-state AUC_{τ} value was 16.5 mg • h/L and was reached after approximately 6 days. Notably, recipients of loading doses (6 mg/kg once every 12 hours on day 1) achieved steady-state plasma concentrations after 1 day.[22,25]

• Voriconazole is widely distributed in humans, with a steady-state volume of distribution of 4.6 L/h.[20-22] The concentration in saliva is about 65% of that in plasma. Plasma protein binding was estimated to be ≈58% and was not correlated with plasma drug concentrations.[21,22] Limited data are available on extravascular distribution of voriconazole, although a case report describes voriconazole concentrations as high as 2.2 mg/L in the cerebrospinal fluid following intravenous administration at 8 mg/kg daily.[26]

• Oral voriconazole pharmacokinetics in 24 patients at risk of fungal infections (haematological malignancies, bone marrow transplantations or solid tumours) appeared to be comparable to those reported in healthy volunteers with respect to nonlinearity, rapid absorption and accumulation.[27]

Metabolism and Elimination

• Elimination of voriconazole is characterised by metabolic clearance, i.e. less than 2% of the parent drug is found in urine.[22] *In vitro* studies using human liver microsomes indicate that voriconazole is metabolised by the hepatic cytochrome P450 (CYP) isoenzymes CYP2C9, CYP2C19 and CYP3A4; CYP2C19 metabolism is the major route.[20,28] The drug is metabolised to the *N*-oxide and several minor metabolites; all metabolites are inactive.[22]

• The elimination half-life for voriconazole is approximately 6 hours,[21,24] and more than 90% of a dose of voriconazole is recovered in faeces and urine within 6 days of administration.[28] After a single radiolabelled oral dose of voriconazole 200mg, 77.9 to 88% is excreted in urine and 18.3 to 25.7% is found in faeces.[28]

Pharmacokinetics in Special Populations

• A study in 24 immunocompromised children (age 2 to 11 years) receiving multiple intravenous doses of voriconazole indicated that elimination of voriconazole occurred at a higher rate in children than adults on a bodyweight basis.[23] According to a population pharmacokinetic study, median steady-state plasma concentrations were similar in children receiving 4 mg/kg once every 12 hours to those in adults receiving 3 mg/kg once every 12 hours (median C_{max} 1.19 vs 1.16 mg/L, respectively).[22] It is therefore suggested that maintenance dosages of 4 mg/kg once every 12 hours are required in children to achieve plasma concentrations comparable to those in adults receiving 3 mg/kg once every 12 hours.[22,23]

• There were no clinically relevant differences in absorption parameters associated with age or gender.[22] Although AUC_{τ} and C_{max} values were 113 and 83% higher in healthy young adult females than males, these differences were not considered relevant based on data from immunocompromised patients who participated in clinical trials.[22] Similarly, differences in these absorption parameters between healthy elderly males (≥65 years of age) and younger adult males (aged 18 to 45 years) were not considered clinically relevant based on results from clinical trials evaluating immunocompromised patients.[22]

• The mean C_{max} value of voriconazole was reduced by ≈20% and oral clearance by ≈50% in six patients with chronic, moderate hepatic impairment (Child Pugh class B) compared with those in six participants with normal hepatic function.[22,29]

Patients with chronic hepatic impairment received a loading regimen of oral voriconazole 400mg once every 12 hours for the first day followed by a reduced maintenance dosage of oral voriconazole 100mg once every 12 hours on days 2 to 6, with a final dose on day 7.[30] Those with normal hepatic function received oral voriconazole at the same times, with the same loading regimen and a standard maintenance dosage of 200mg once every 12 hours.[29] There are currently no pharmacokinetic data available in patients with severe hepatic impairment (Child Pugh class C).[22]

• With oral or intravenous voriconazole there was no clinically relevant difference in systemic exposure in patients with mild to severe renal impairment compared with participants with normal renal function.[22] However, seven patients with moderate renal impairment [creatinine clearance 1.8 to 3 L/h (30 to 50 ml/min)] receiving intravenous voriconazole (6 mg/kg once every 12 hours for 1 day followed by 3 mg/kg once every 12 hours for 5.5 days) showed accumulation of the vehicle; mean AUC and C_{max} values for the vehicle increased 4-fold and by ≈50%, respectively.

Drug Interactions

• Voriconazole has been shown to inhibit CYP2C9, CYP2C19 and, to a lesser extent, CYP3A4.[20] Thus, inhibitors or inducers of these enzymes may alter pharmacokinetic parameters of voriconazole and *vice versa*. Although currently there are no clinical data available, voriconazole may increase the plasma concentration of several agents including benzodiazepines, calcium channel antagonists, HMG-CoA reductase inhibitors and vinca alkaloids.[22] Similarly, concomitant administration of voriconazole with non-nucleoside reverse transcriptase inhibitors or HIV protease inhibitors may potentially alter the pharmacokinetics of either drug.[22]

• Exposure to the CYP3A4 substrates cyclosporin,[31] phenytoin,[32] omeprazole,[33,34] sirolimus[22] or tacrolimus[35] has been shown to be markedly increased when these drugs are coadministered with voriconazole.

• Although no data are currently available, concomitant administration of voriconazole with the CYP3A4 substrates terfinadine, astemizole, cisapride, pimozide or quinidine is predicted to increase systemic exposure to these substrates and thus potentially prolong the QT interval.[22]

• In healthy volunteers, coadministration of voriconazole potentiated the prothrombin time induced by warfarin (CYP2C9 substrate) in a randomised, double-blind, cross-over study.[36] Recipients of oral voriconazole 300mg once every 12 hours for 12 days plus a concomitant single dose of warfarin 30mg at day 12 experienced a 2-fold increase in prothrombin time compared with that in volunteers receiving placebo plus warfarin.[36] Currently no data are available for the concomitant administration of voriconazole with oral coumarin anticoagulants, but voriconazole may also potentially increase the plasma concentrations of these agents and thereby increase the prothrombin time.[22]

• Coadministration of voriconazole with phenytoin,[32] rifampicin[37] or rifabutin[37] decreased systemic exposure to voriconazole in healthy volunteers. Furthermore, steady-state C_{max} and AUC_{τ} values of rifabutin increased approximately 2-fold with concomitant voriconazole.[22]

• There were no clinically relevant effects on the pharmacokinetic parameters of either agent when voriconazole was coadministered with prednisolone,[22] digoxin,[22,38] indinavir[22,39] or mycophenolic acid.[22,40]

3. Therapeutic Trials

The clinical efficacy of voriconazole for the treatment of invasive aspergillosis has been evaluated in adults and adolescents (aged ≥12 years) who were immunocompromised.[41-44] Children enrolled in a compassionate use program were also evaluated.[45] A complete response was defined as the resolution of all clinical signs and symptoms and a >90% improvement in radiological assess-

ment, and a partial response as a clinical improvement and at least a 50% improvement in the radiological assessment.[41,44] The typical treatment regimen with voriconazole was intravenous voriconazole 6 mg/kg once every 12 hours for 1 day followed by a maintenance dosage of 4 mg/kg once every 12 hours. Patients could be switched to oral voriconazole 100 or 200mg once every 12 hours based on bodyweight (<40kg or ≥40kg, respectively).

In Adults

• A randomised, nonblind, multicentre trial in 392 patients (aged ≥12 years; mean age 48.5 years) with invasive aspergillosis compared the efficacy of voriconazole with that of amphotericin B.[41] Patients received intravenous voriconazole (typical regimen) or intravenous amphotericin B (1 to 1.5 mg/kg/day) for up to 12 weeks. Patients who failed to respond or showed toxicity to the initial randomised therapy could be switched to other licensed antifungal therapy (including amphotericin B deoxycholate, liposomal amphotericin B, itraconazole or other unspecified agents). Median duration of initial randomised treatment was 77 days for voriconazole and 11 days for amphotericin B. Acute leukaemia was the major underlying condition in these patients (40.3% of voriconazole recipients and 45.1% of those receiving amphotericin B); 25.7 and 22.6% of patients, respectively, had undergone allogenic haematopoietic-cell transplantation. Most participants (≈83%) had pulmonary infections.

• In this study, a higher percentage of voriconazole than amphotericin B recipients had a complete or partial clinical response after 12 weeks of treatment (primary endpoint) in the modified intention-to-treat population (i.e. patients who received at least one dose of study drug) [figure 1].[41] A successful outcome (complete or partial response) was achieved by markedly more voriconazole recipients than those receiving amphotericin B (52.8 vs 31.6% of patients; 95% CI 10.4–32.9%).[41] In addition, the 12-week survival rate for patients initially receiving voriconazole was higher than for those initially receiving amphotericin B (hazard ratio 0.59, 95% CI 0.40–0.88) [figure 1].[41]

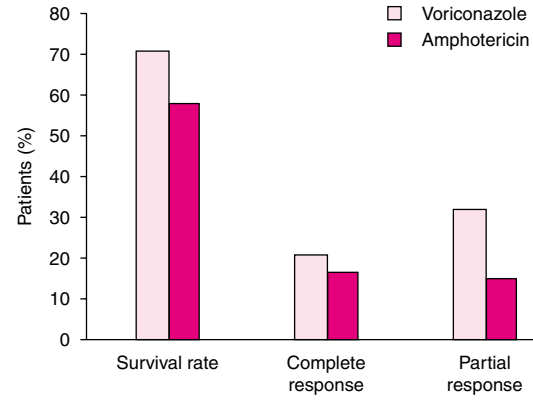


Fig. 1. Comparative efficacy of voriconazole and amphotericin B in the treatment of invasive aspergillosis.[41] In a randomised, nonblind study, 392 patients (≥12y of age) received intravenous voriconazole (6 mg/kg once every 12 hours on the first day followed by 4 mg/kg once every 12 hours for at least 7 days; patients could then be switched to oral voriconazole 200mg twice daily at the investigators' discretion) or intravenous amphotericin B (1 to 1.5 mg/kg/day) for up to 12 weeks. Patients who failed to respond or showed toxicity to the initial randomised therapy could be switched to other licensed antifungal therapy (including amphotericin B deoxycholate, liposomal amphotericin B, itraconazole and other unspecified agents).[41] Median treatment duration for the initial randomised therapy was 77 days for voriconazole and 11 days for amphotericin B.

• In 116 immunocompromised patients (aged ≥14 years, median age 52 years) with acute invasive aspergillosis, voriconazole treatment resulted in a successful outcome in 48% of recipients.[44] Forty-eight percent of participants had previously received antifungal treatment (amphotericin B, itraconazole or flucytosine). Patients were treated for up to 24 weeks.[44]

• Similarly, 53% of 102 patients with neutropenia and acute invasive aspergillosis had a complete (17% of patients) or partial (36%) response to voriconazole treatment in another noncomparative study.[42]

• A successful outcome was achieved by 41% of 51 patients with invasive aspergillosis receiving

voriconazole in a multicentre trial.[43] Voriconazole was administered orally or intravenously; the dosage and treatment duration were not reported in the abstract. Aspergillosis was diagnosed as 'definite' in 73% of these patients and 'probable' in 27%. The most frequent infection was pulmonary.[43]

• Small studies[42,46] (n < 20 patients per study) and case reports[26,47-50] have confirmed the efficacy of voriconazole treatment in patients with invasive aspergillosis.

In Children

• The efficacy of voriconazole in the treatment of invasive fungal infections (72% *Aspergillus* spp.) has also been assessed in 58 children (aged 9 months to 15 years; mean age 8.2 years) enrolled in a compassionate use program, all of whom had failed to respond to or were intolerant of previous antifungal therapy (drugs not specified).[45] A complete or partial response was achieved by 45% of children and a further four children (7%) had a stable response. The success rate (complete or partial response) was highest in children with chronic granulomatous disease (62%) and lowest in those with haematological malignancies (33%).[45] The median duration of treatment was 93 days.

4. Tolerability

• Voriconazole was generally well tolerated in adults and adolescents participating in clinical trials discussed in section 3. The most commonly reported adverse event with voriconazole was transient visual disturbances, experienced by 8 to 44% of patients.[41,42,44] According to the manufacturer's prescribing information, approximately 30% of patients experience altered/enhanced visual perception, blurred vision, colour vision changes and/or photophobia.[22] These visual disturbances were generally transient and rarely resulted in discontinuation of treatment.[22]

• Six percent (86 of 1493 patients) of voriconazole recipients experienced treatment-related skin rashes in clinal trials.[22] These rashes were generally mild to moderate in severity. There have been very rare cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme reported.[22,51]

• Voriconazole was generally better tolerated than amphotericin B in a nonblind trial in 392 patients (see section 3 for dosages).[41] Voriconazole recipients experienced significantly fewer treatment-related adverse events than those receiving amphotericin B (343 vs 421 adverse events; $p = 0.02$).[41] Visual disturbances occurred more frequently in voriconazole than amphotericin recipients (44.8 vs 4.3%; $p < 0.001$); however, these visual disturbances were all transient and resolved spontaneously. Significantly fewer patients experienced chills and/or fever in the voriconazole than amphotericin B groups (3.1 vs 24.9%; $p < 0.001$), but there was a trend for more patients to experience skin reactions with voriconazole treatment (8.2 vs 3.2%; $p = 0.05$). Notably, significantly fewer voriconazole recipients experienced serious treatment-related events than amphotericin B recipients (13.4 vs 24.3% of patients; $p < 0.008$); these were mainly liver-function abnormalities in the voriconazole group (7 patients) and renal impairment in amphotericin recipients (19 patients).[41]

• Pooled data from 1053 patients who participated in ten clinical trials indicated that the absolute risk for liver abnormalities during voriconazole treatment was low, with maximum occurrences of 10, 8, 5 and 14% for elevations of AST, ALT, alkaline phosphatase (ALP) or bilirubin, respectively.[52] The predicted increase in the odds of an AST, ALT, ALP or bilirubin abnormality, however, was estimated to be 13%, 7%, 16% and 17%, respectively, for every 1 mg/L increase in plasma voriconazole concentration.[52]

• Forty percent of children (aged ≤15 years) experienced at least one treatment-related adverse event in 58 children with fungal infections enrolled in a compassionate use program.[45] The most commonly (>5% of patients) reported adverse events were elevations of serum transaminase or bilirubin levels (8 patients; 13.8%), skin rash (13.8%), ab-

normal vision (5.2%) and photosensitivity reactions (5.2%). The majority of these adverse reactions were transient and had resolved by the end of treatment, with three children discontinuing treatment because of a treatment-related adverse events.

5. Dosage and Administration

Intravenous voriconazole, with or without a switch to oral administration, is recommended for the treatment of adults with invasive aspergillosis.[22,53] The drug may also be used for the treatment of patients with infections caused by *Fusarium* spp. and *Scedosporium apiospermum* who are refractory to or intolerant of other antifungal therapy.[22]

The intravenous regimen consists of loading doses of 6 mg/kg once every 12 hours for the first day followed by a maintenance dosage of 4 mg/kg once every 12 hours; the maximum rate of infusion is 3 mg/kg per hour.[22,53] Patients may be switched to a maintenance dosage of oral voriconazole 200mg once every 12 hours in those weighing at least 40kg or 100mg once every 12 hours in those weighing less than 40kg.[22,53]

6. Voriconazole: Current Status

Voriconazole, a triazole broad-spectrum antifungal agent, is indicated in the US for the treatment of adult patients with invasive aspergillosis and for the treatment of infections caused by *Fusarium* spp. and *S. apiospermum* in those who are intolerant of or refractory to other antifungal agents.[22] In Europe, the drug is recommended for the treatment of adult patients with invasive aspergillosis, those with serious fungal infections caused by *Fusarium* spp. and *Scedosporium* spp., or those with fluconazole-resistant serious invasive Candida infections; voriconazole should primarily be administered to immunocompromised patients with progressive, possibly life-threatening infections.[53] In clinical trials in immunocompromised adults with aspergillosis, approximately 50% of voriconazole recipients achieved a complete or partial response. The drug was generally well tolerated, with the most common treatment-related adverse events being visual disturbances and skin rash.

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