For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Voriconazole Tablets IP 200 mg

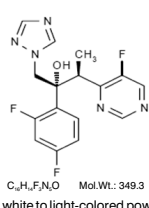
GALENVOR™

COMPOSITION

Each film coated tablet contains:
Voriconazole IP 200 mg
Colour: Titanium Dioxide IP

DESCRIPTION

Galenvor™ (voriconazole tablets), a triazole antifungal agent, is available as film coated tablets for oral administration. Voriconazole is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4- pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol. The structural formula is:



$C_{16}H_{14}F_3N_5O$ Mol.Wt.: 349.3

Voriconazole drug substance is a white to light-colored powder.

CLINICAL PHARMACOLOGY

Mechanism of action:

Voriconazole is a broad spectrum triazole antifungal agent. Its mode of action is inhibition of fungal cytochrome P450-rnediated 14 alpha-sterol demethylation, an essential step in ergosterol biosynthesis.

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*.

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However once these results become available, anti-infective therapy should be adjusted accordingly.

Pharmacokinetics

Absorption

The pharmacokinetic properties of voriconazole are similar following administration by the oral and intravenous routes. Maximum plasma concentrations (Cmax) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high-fat meals, the mean Cmax and AUCτ are reduced by 34% and 24%, respectively when administered as a tablet and by 58% and 37% respectively when administered as the oral suspension.

In healthy subjects, the absorption of voriconazole is not affected by co- administration of oral ranitidine, cimetidine, or omeprazole, drugs that are known to increase 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% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 mg or 300 mg (approximate range: 0.9-15 μg/mL). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radio labelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (> 94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

INDICATIONS AND USAGE

Galenvor™ is indicated for use in the treatment of the following fungal infections:

- Invasive aspergillosis. In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There were a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. Fumigatus*.
- Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds. Esophageal candidiasis.
- Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and Fusarium spp. including *Fusarium* solani, in patients intolerant of, or refractory to, other therapy.
- Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CONTRAINDICATIONS

Galenvor™ is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between **Galenvor™** (voriconazole) and other azole antifungal agents. Caution should be used when prescribing **Galenvor™** to patients with hypersensitivity to other azoles.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with **Galenvor™** are contraindicated since increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*.

Coadministration of **Galenvor™** with sirolimus is contraindicated because **Galenvor™** significantly increases sirolimus concentrations in healthy subjects.

Coadministration of **Galenvor™** with rifampin, carbamazepine and long-acting barbiturates is contraindicated since these drugs are likely to decrease plasma voriconazole concentrations significantly.

Coadministration of **Galenvor™** with high-dose ritonavir (400 mg Q12h) is contraindicated because ritonavir (400 mg Q12h) significantly decreases plasma voriconazole concentrations in healthy subjects. Coadministration of voriconazole and low-dose ritonavir (100 mg Q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Coadministration of **Galenvor™** with rifabutin is contraindicated since **Galenvor™** significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations.

Coadministration of **Galenvor™** with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because **Galenvor™** may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.

WARNINGS

Visual Disturbances: The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored.

Hepatic Toxicity:

In clinical trials, there have been uncommon 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 hematological malignancy). 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 function: Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during voriconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of voriconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole.

Pregnancy Category D:

Voriconazole can cause fetal harm when administered to a pregnant woman.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

Arrhythmias and QT Prolongation

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as *torsade de pointes*), cardiac arrests and sudden deaths in patients taking voriconazole. These cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

Voriconazole should be administered with caution to patients with these potentially pro-arrhythmic conditions.

Rigorous attempts to correct potassium, magnesium and calcium should be made before starting voriconazole.

Infusion Related Reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Teratogenic Effects

Pregnancy category D

Voriconazole can cause fetal harm when administered to a pregnant woman.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers

The excretion of voriconazole in breast milk has not been investigated. Voriconazole should not be used by nursing mothers unless the benefit clearly outweighs the risk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

The overall safety profile of the elderly patients was similar to that of the young, so no dosage adjustment is recommended.

DRUG INTERACTIONS

Voriconazole is metabolized by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively.

Therefore there is potential for voriconazole to increase the plasma levels of substances metabolized by these CYP450 isoenzymes.

Rifampicin, Carbamazepine and phenobarbital *are potent* CYP450 inducers hence Coadministration of voriconazole and rifampicin, carbamazepine and phenobarbital is contra-indicated.

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contra-indicated, since increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of *torsades depointes*

Sirolimus, Ergot alkaloids (ergotamine and dihydroergotamine) (CYP3A4 substrate): Coadministration of voriconazole and Sirolimus, ergot alkaloids are contra-indicated.

Cyclosporin (CYP3A4 substrate): In stable, renal transplant recipients, when initiating voriconazole in patients already receiving cyclosporin, it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

Tacrolimus (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1 mg/kg single dose) Cmax and AUCt (area under the plasma concentration time curve to the last quantifiable measurement) by 117% and 221%, respectively. When initiating voriconazole in patients already receiving 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.

Oral anticoagulants:

Warfarin (CYP2C!) substrate): Coadministration of voriconazole with warfarin increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are co-administered.

Other oral anticoagulants e.g. phenprocoumon, acenocoumarol (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

Sulphonylureas (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

Statins (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro (human* liver microsomes). Therefore, voriconazole is likely to increase plasma levels of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin levels have been associated with rhabdomyolysis.

Benzodiazepines (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma levels of benzodiazepines, that are metabolized by CYP3A4 (midazolam, triazolam and alprozolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepines be considered during coadministration.

Vinca Alkaloids*:* (CYP3A4 substrate): Although not studied, voriconazole may Increase the plasma levels of vinca alkaloids (e.g. vincristine and vinblastine) and lead in neurotoxicity. It is therefore recommended dose adjustment of the vinca alkaloids be considered.

Prednisolone (CYP3A4 substrate): Voriconazole increased Cmax and AUC, of prednisolone (60mg) single dose by 11% and 34% respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): Voriconazole had no significant effect on Cmax and AUC of digoxin (0.25 mg once daily).

Mycophenolic acid **(UDP-glucuronyl transferase substrate):** Voriconazole had no effect on the Cmax and AUCt of mycophenolic acid (1 g single dose).

Two-way interactions

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk.

Carotid monitoring of plasma phenytoin levels is recommended when phenytoin is coadministered with voriconazole.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 3 mg/kg to 5mg /kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg).

Rifabutin (CYP450 inducer): Concomitant use of voriconazole and rifabutin is contra-indicated. Rifabutin decreased the Cmax and AUC of voriconazole at 200 mg twice daily by 69% and 78% respectively. During coadministration with rifabutin, the Cmax and AUC, of voriconazole at 350 mg twice daily were 96% and 68% of the levels when administered alone at 200 mg twice daily. At a voriconazole dose of 400 mg twice daily, Cmax and AUC were 104% and 87% higher, respectively, compared with voriconazole alone at 200 mg twice dally voriconazole al 400 mg twice daily increased Cmax and AUC, of rifabutin by 195% and 331%, respectively.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40 mg once daily) increased voriconazole Cmax and AUC, by15% and 41%, respectively. No dosage adjustment of voriconazole is recommended.

Voriconazole increased omeprazole Cmax and AUC, by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved.

The metabolism of other proton pump inhibitors, which are CYP2C19 substrates, may also be inhibited by voriconazole.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800 mg three times daily) had no significant effect on voriconazole Cmax and AUC.

Voriconazole did not have a significant effect on Cmax and AUC, of indinavir (800 mg three times daily).

Other HIV protease Inhibitors (CYP3A4 Inhibitors): in vitro studies suggests that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir). *In vitro* studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors.

However results of the combination of voriconazole with other HIV protease inhibitors cannot be predicted in humans only from *in vitro* studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy.

Non-nucleoside reverse transcriptase inhibitors **(NNRTI)** (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine and efavirenz. Although not studied, the metabolism of voriconazole may be induced by efavirenz and nevirapine. Voriconazole may also inhibit the metabolism of NNRTIs. Due to the lack of *in vivo* studies, patients should be carefully monitored for any occurrence of drug toxicity and or lack of efficacy during the co-administration of voriconazole and NNRTIs.

ADVERSE REACTIONS

Overview

The most frequently reported adverse events (all causalities) were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances.

Visual disturbances:

Voriconazole treatment-related visual disturbances are common. The visual disturbances were generally mild and rarely resulted in discontinuation. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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

Dermatological Reactions:

Dermatological reactions were common in the patients treated with voriconazole. The mechanism underlying these dermatologic adverse events remains unknown. The majority of rashes were of mild to moderate severity. Cases of photosensitivity reactions appear to be more likely to occur with long-term treatment. Patients have rarely developed serious cutaneous reactions. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of voriconazole. It is recommended that patients avoid strong, direct sunlight during voriconazole therapy.

Body as a Whole:

Abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction, ascites, asthenia, back pain, chest pain, cellulitis, edema, face edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain

Cardiovascular:

Atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, endocarditis, extrasystoles, heart arrest, hypertension, hypotension, myocardial infarction, nodal arrhythmia, palpitation, phlebitis, postural hypotension, pulmonary embolus, QT interval prolonged, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophlebitis, vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including *torsade de pointes*).

Digestive:

Anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, diarrhea, duodenal ulcer perforation, duodenitis, dyspepsia, dysphagia, dry mouth, esophageal ulcer, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation, intestinal ulcer, jaundice, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema

Endocrine:

adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism

Hemic and Lymphatic:

Agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, leukopenia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, thrombocytopenia, thrombotic thrombocytopenic purpura.

Metabolic and Nutritional:

Albuminuria, BUN increased, creatine phosphokinase increased, edema, glucose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hypophosphatemia, peripheral edema, uremia.

Musculoskeletal:

Arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia, myopathy, osteomalacia, osteoporosis.

Nervous System:

Abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, dizziness, encephalitis, encephalopathy, euphoria, Extrapyramidal Syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo.

Respiratory System:

C*o*ugh increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration.

Skin and Appendages:

Alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanosis, photosensitivity skin reaction, pruritus, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, sweating, toxic epidermal necrolysis, urticaria.

Special Senses:

Abnormality of accommodation, blepharitis, color blindness, conjunctivitis, corneal opacity, deafness, ear pain, eye pain, eye hemorrhage, dry eyes, hypoacusis, keratitis, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, optic neuritis, otitis externa, papilledema, retinal hemorrhage, retinitis, scleritis, taste loss, taste perversion, tinnitus, uveitis, visual field defect.

Urogenital:

Aanuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria, epididymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, urinary incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrhage

DOSAGE AND ADMINISTARTION:

Galenvor™ tablets should be taken at least one hour before, or one hour following, a meal.

Use in Adults:

Therapy must be initiated with the specified loading dose regimen of either oral or intravenous **Galenvor™** to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%), switching between intravenous and oral administration is appropriate when clinically indicated.

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

	Intravenous	Oral	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose regimen (first 24 hrs)	(6mg/kg every 12 hrs (for the first 24hrs)	400 mg every 12hrs (for the first 24hrs)	200 mg every 12hrs for the first 24hrs)
Maintenance Dose (after first 24 hrs) Prevention of breakthrough infections	3mg/kg every 12hrs	200 mg twice daily	100 mg twice daily
Maintenance Dose (after first 24 hrs) Prevention of breakthrough infections	3mg/kg every 12hrs	200 mg twice daily	100 mg twice daily

If patient response 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 response is inadequate, the maintenance dose may be increased to 4 mg/kg twice daily for intravenous administration.

If patients are unable to tolerate treatment at these higher doses, reduce the intravenous dose to the original maintenance dose, 3 mg/kg twice daily.

If patients are unable to tolerate treatment at these higher doses, 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 co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously twice daily.

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg lo 400 mg orally, twice daily (l00 mg to 200 mg orally twice daily in patients less than 40 kg).

Treatment duration depends upon patients clinical and mycological response.

Use in the elderly

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment.

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min), accumulation of the intravenous vehicle, a derivative (s) of beta-dextrin, occurs.

Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to these patients 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.

Voriconazole is haemodialysed with a clearance of 121 mL/min. A four-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

The intravenous vehicle, a derivative(s) of beta-dextrin, occurs is haemodialysed with a clearance of 55 mL/min.

Use in patients with hepatic impairment

No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT), but continued monitoring of liver function tests for future elevations is recommended.

It is recommended that half the standard loading dose regimens be used and that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.

Galenvor™ has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Galenvor™ has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice. Patients with hepatic impairment must be carefully monitored for drug toxicity.

Use in children

Safety and effectiveness in pediatric subjects below the age of 2 years has not been established. Therefore, voriconazole is not recommended for children less than 2 years of age.

Limited data are currently available to determine the optimal posology.

However, the following regimen has been used in pediatric studies.

	Intravenous	Oral
Loading Dose regimen (First 24hrs)	**6mg/kg every 12hrs** (for the first 24hrs)	**6mg/kg every 12hrs** (for the first 24hrs)
Maintenance Dose (After First 24hrs)	**4mg/kg every 12hrs**	**4mg/kg every 12hrs**

If a child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50 mg tablets.

The pharmacokinetics and tolerability of higher doses have not been characterized in pediatric populations.

Adolescents (12 to 16 years of age):

Should be dosed as adults.

Duration of Treatment

Treatment duration depends on the patient's clinical and mycological response, the duration of oral and intravenous voriconazole treatment in the clinical studies ranged from 12 weeks to more than 6 months.

OVERDOSAGE

In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

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

STORAGE :

Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

HOW SUPPLIED

Galenvor

4 Tablets pack in a blister, 1 blister in a mono carton with package insert.

xxxxxxxx

SHELF LIFE

24 months

GALENGEN

Marketed by :
Galengen Lifesciences Pvt. Ltd.
First floor, South Wing, No: 51, 11th Cross Street, 9th Main Road, Dhandeeswaram Nagar, Velachery, Chennai-600042.
TM-Trade Mark Under Registration

Manufactured by :
Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of
Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL, Ranipur, Haridwar-249 403, Uttarakhand.