CANDIVOR
(Voriconazole for Injection 200 mg/vial)

1. Name of the finished pharmaceutical product

INN Name: Voriconazole for Injection 200 mg/vial
Trade Name: CANDIVOR

Strength: 200 mg/Vial

Pharmaceutical form:

Injection

2. Qualitative and quantitative composition

Each vial contains Voriconazole Ph.Eur equivalent to Voriconazole 200mg, 3200 mg of Hydroxypropyl beta-cyclodextrin USP, Hydrochloric acid may have been used to adjust pH.

3. Pharmaceutical formDosage form:

Injection

Description: The proposed Voriconazole for Injection 200 mg/vial are available as a white to off- white lyophilized cake filled in 30 mL clear, Type I molded glass and sealed with grey bromobutyllyophilisation rubber stopper and white colored flip off seal.

4. Clinical particulars

4.1. Therapeutic indications

Voriconazole For Injection is indicated for use in treatment of the following conditions:

- Treatment of invasive Aspergillosis
- Treatment of fluconazole-resistant serious invasive candida infection (including C.krusei)
- Esophageal candidiasis.
- Serious fungal infection caused by Scedosporium spp. (A sexual form of Pseudallescheria body) and Fusarium spp., including Fusarium solani in patient's intolerant of or refractoryto 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 result of the cultures and other laboratory studies are known however once these results become available, an liable therapy should be adjusted accordingly.

4.2. Posology and method of administration

Voriconazole I.V. for Injection requires reconstitution to 10 mg/mL and subsequent dilution to 5 mg/mL or less prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over1 to 2 hours.

4.3. Contraindications

Voriconazole For Injection is contraindicated in patients with known hypersensitivity to Voriconazole for Injection or to any of the excipients.

Co-administration of CY3A4 substrates, terfenadine, astemizole cisapride, pimozide or quinidine since increased plasma concentration of these drugs can lead to QTc prolongation and rareoccurrences of torsades de points.

Coadministration of Voriconazole for Injection with sirolimus is contraindicated because Voriconazole for Injection significantly increases plasma concentrations sirolimus.

Co-administration of Voriconazole for Injection with rifampin, carbamazepine and long-acting barbiturates (e.g., phenobarbital mephobarbital) is contraindicated since these drugs are likely to decrease Plasma Voriconazole for Injection concentrations significantly.

Co-administration of Voriconazole for Injection with ritonavir (400 mg twice daily) is contraindicated because ritonavir significantly decreases plasma Voriconazole for Injection.

Co-administration of Voriconazole for Injection with rifabutin is contraindicated since Voriconazole for Injection significantly increases rifabutin plasma concentration and nlabulin also significantly decreases VORICONAZOLE FOR INJECTION plasma concentrations.

Co-administration of Voriconazole for Injection with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because Voriconazole for Injection may increase the plasma concentration of ergot alkaloids which may lead to ergotism.

4.4. Special warnings and precautions for use

Caution should be used when prescribing VORICONAZOLE FOR INJECTION to patients with hypersensitivity to other azoles.

Some azoles including VORICONAZOLE FOR INJECTION have been associated with prolongation of QTc interval. There have been rare cases of torsades de pointers in patients taking VORICONAZOLE FOR INJECTION these reports involved seriously ill patients with multiple

confounding risk factors such as history of cardiotoxic chemotherapy; cardiomyopathy, hypokalaemia and concomitant medication that may have been contributory. VORICONAZOLE FOR INJECTION should be administered with caution to patients with these potentially proarrhythmic conditions such as congenital or acquired or QTc prolongation, cardiomyopathy in particular when heart failure is present, sinus bradycardia, existing symptomatic arrthymias and concomitant medication that is known to prolong QTc interval.

If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should mentioned VORICONAZOLE FOR INJECTION may cause vision changes, therefore patients on this drug should be advised to avoid potentially hazardous tasks, such as driving or operating machinery, if they perceive any change in vision.

There have been uncommon cases of serious hepatic reactions during treatment with VORICONAZOLE FOR INJECTION (including clinical hepatitis, cholestasis failure, including fatalities) liver function test should be evaluated at the start of and during the course of VORICONAZOLE FOR INJECTION therapy. Patients who develop abnormal liver function test during VORICONAZOLE FOR INJECTION therapy should be monitored for the development ofmore severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VORICONAZOLE FOR INJECTION must be considered clinical signs and symptoms consistent with liver disease develop that may be attributable to VORICONAZOLE FOR INJECTION.

VORICONAZOLE FOR INJECTION labels contain lactose and should not be given to patients with rare hereditary problems of galactose in clearances. Lapplactose deficience/ or glucosegalactose malabsorption.

Electrolytes distrubances such as hypokalemia, hypomagnesemia and hypocalcemia should be monitored and corrected, if necessary, prior to initiation and during VORICONAZOLE FOR INJECTION therapy.

Anaphylactic type reactions including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have been observed during administration of intravenous infusion of VORICONAZOLE FOR INJECTION in healthy

subject's symptoms appeared immediate upon initiating the infusion. Depending on the diversity of symptoms consideration should be given to stopping the treatment.

Acute renal failure has been observed in severely if patients undergoing treatment with VORICONAZOLE FOR INJECTION patients being treated with are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function. This should include laboratory evaluations, particularly serum k creatinine.

Patients have rarely developed serious cutaneous reactions. Such as Stevens – Johnson syndrome toxic epidermal necrolysis and erythema multiforme doing treatment with VORICONAZOLE FOR INJECTION. If patients develop a rash they should be monitored closely and consideration given to discontinuation of VORICONAZOLE FOR INJECTION, VORICONAZOLE FOR INJECTION has been infrequently associated with photosensitivity skin reaction. Especially during long term therapy it is recommended that patients avoid strong direct sunlight during VORICONAZOLE FOR INJECTION therapy.

4.5. Interaction with other medicinal products and other forms of interaction

Voriconazole For Injection is metabolised by the human cytochrome P450 enzymes CYP2C19, CYP2C9 and CYP3A4 Inhibitors or inducers of these three enzymes may increase or decrease Voriconazole For Injection systemic exposure (plasma concentrations) respectively.

Co-administration of Voriconazole For Injection with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because Voriconazole For Injection may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.

Co-administration of Voriconazole For Injection at 400mg twice daily with rifabutin 300mg twice daily increased the C_{max} and AUC of rifabutin by an average of 3 times and 4 times respectively compared to when rifabutin is given alone. Co-administration of Voriconazole For Injection and rifabutin is contraindicated.

Cimetidine (400mg twice daily) increased Voriconazole For Injection steady C_{max} and AUC by an average of 18% and 23% respectively following oral doses of 200mg

Voriconazole For Injection. No dosage adjustment of Voriconazole For Injection concentrations significantly.

Repeat dose administration of oral Voriconazole For Injection increased the C_{max} and AUC of sirolimus and average of 7 fold and 11 fold respectively, in healthy subjects co-administration of Voriconazole For Injection and sirolimus is this contraindicated.

Concomitant administration of Voriconazole For Injection with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QTc prolongation and are occurences of torsade de points co-administration of Voriconazole For Injection with these drugs is thus contraindicated.

In stable renal transplant recipients receiving chronic cyclosporine therapy Voriconazole For Injection increased cyclosporine C_{max} and AUC by atleast 1.1 and 1.7 times respectively, when initiating therapy with Voriconazole For Injection in patients already receiving cyclosporine it is recommended that the cyclosporine dose be reduced to one half of the original dose and followed with frequent monitoring of cyclosporine blood levels. Increased cyclopedia levels have been associated with nephrotoxicity when Voriconazole For Injection is discontinued, cyclosporine levels should be frequently monitored and the dose is increased as necessary.

Repeat oral dose administration of Voriconazole For Injection (400mg every 12 hours on day 1 and 200mg every 12 hours for 6 days) increased tacrolimus (0.1mg/kg single dose) C_{max} and AUC by an average of 2 fold and 3 fold respectively when initiating therapy with Voriconazole For Injection in patients already receiving tacrolimus it is recommended that the tacrolimus dose be reduced to one third of the original dose and followed with frequent monitoring of the tacrolimus blood levels increased tacrolimus level have been associated with nephrotoxicity. When is a discounted tacrolimus level should be carefully monitored and the dose increased as necessary.

Co-administration Voriconazole For Injection (300mg twice daily) with warfarin (300mg single dose) significantly increased maximum prothrombin time by approximately 2 times

that of placebo close monitoring of prothrombin time or other suitable anticoagulation test is recommended if warfarin and Voriconazole For Injection are co-administered and the warfarin dose adjusted accordingly.

Although not studied *invitro- invivo*, Voriconazole For Injection may increase the plasma concentrations of coumarin anticoagulants (e.g., phenprocoumon, acenocoumarol) and there fore may cause an increasing in prothrombin time if patients receiving coumarin preparations are treated simultaneously with Voriconazole For Injection the prothrombin time or other suitable anticoagulation tests should be mentioned at close intervals and the dosage of anticoagulants adjusted accordingly.

Although not studied clinically Voriconazole For Injection has been shown to inhibit lovastatin metabolism in vitro (human liver microsomes) therefore Voriconazole For Injection is likely to increase the plasma concentrations of stains that are metabolized by CYP3A4 it is recommended that dose adjustment of the statin be considered during co-administration increased stain concentration in plasma have been associated with rhabdomyolysis.

Although not studied clinically Voriconazole For Injection have been shown to inhibit midazolam metabolism *invitro* therefore Voriconazole For Injection is likely to increase the plasma concentrations of benzodiazepines that are metabolite by CYP3A4 (e.g. midazolam, triazolam and alprazolam) therefore Voriconazole For Injection may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4 frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administrations dose adjustment of the calcium channel blocker may be needed.

Although not studied Voriconazole For Injection may increase plasma concentration, if sulphonylureas (e.g tolbutamide, glipizide and glyburide) and therefore cause hypoglycemia frequent monitoring of blood glucose and appropriate adjustments (i.e reduction of the sulphonylurease is recommended during co-administration.

Although not studied Voriconazole For Injection may increase the plasma concentrations

of the Vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity therefore it is recommended that dose adjustment of the vinca alkaloid be considered C_{max} and AUC of prednisolone (60mg single dose) by an average of 11% and 34% respectively. No dosage adjustment is recommended.

Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC of administered Voriconazole For Injection (200 mg every 12 hour for 14 days) by an average of 50% and 70% respectively. Repeat dose administration of Voriconazole For Injection (400 mg twice daily) increased the steady C_{max} and AUC of phenytoin C_{max} and AUC estimates when phenytoin is given without Voriconazole For Injection. Therefore frequent monitoring of plasma phenytoin concentrations and phenytoin related adverse effects is recommended when phenytoin is co-administered with Voriconazole For Injection.

Co-administered of omeprazole (40 mg once daily) with oral VORICONAZOLE FOR INJECTION (400 mg every 12 hours for day 1 then 200 mg every 12 hours for 9 days) increased the state C_{max} and AUC of VORICONAZOLE FOR INJECTION by an average of 15% and VORICONAZOLE FOR INJECTION with omeprazole (40 mg once daily) significantly increased the steady state C_{max} and AUC of omeprazole an average of 2 times and 4 times respectively. When initiating VORICONAZOLE FOR INJECTION in patients already receiving omeprazole dose of 40 mg or greater it is recommended that the omeprazole dose de reduced by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by VORICONAZOLE FOR INJECTION and may result in increased plasma concentration of these drugs.

Co-administration of VORICONAZOLE FOR INJECTION with ritonavir (400 mg twice daily) is contraindicated because ritonavir significantly decreases plasma VORICONAZOLE FORINJECTION C_{max} and AUC following repeat dose administration of VORICONAZOLE FOR INJECTION (200 mg every 12 hour for 17 days) in healthy subjects. repeat dose administration ofVORICONAZOLE FOR INJECTION (200 mg twice daily for 7 days) did not have a significant effect on steady state C_{max} and AUC of indinavir following repeat dose administration (200 mg twice daily for 7 days) did not have

a significant effect on steady state C_{max} and AUC of indinavir following repeat dose administration (800 mg TID or 7 days) in healthy subjects.

In-vitro studies (human liver microsomes) suggest that VORICONAZOLE FOR INJECTION may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir).

In-vitro studies (human liver microsomes) also show that the metabolism of VORICONAZOLE FOR INJECTION may be inhibited by HIV Protease inhibitors. Patients should be frequently monitored for drug toxicity during the co-administration of VORICONAZOLE FOR INJECTION and HIV protease inhibitors.

In-vitro studies (human liver microsomes) show that the metabolism of VORICONAZOLE FOR INJECTION may be inhibited by non-nucleoside reverse transcriptase inhibitors (NNRTI) (e.g. delavirdine and efavirenz). VORICONAZOLE FOR INJECTION may also inhibit the metabolismof an NNRTI.

VORICONAZOLE FOR INJECTION had no significant effect on steady state C_{max} and AUC of digoxin (0.25 mg once daily for 10 days). VORICONAZOLE FOR INJECTION had no significant effect on the C_{max} and AUC of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1g single oral dose of Mycophenolate mofetil. Ranitidine had no significant effect on VORICONAZOLE FOR INJECTION C_{max} and AUC following oral dose 200mg twice daily. Co-administration of erythromycin (CYP 34A inhibltor; 19 every 12h for 7 days) or azithromycin (500 mg four times a day for 3 days) with VORICONAZOLE FOR INJECTION 200 mg twice daily for 14 days had no significant effect on VORICONAZOLE FOR INJECTION steady state C_{max} and AUC in healthy subjects.

4.6.Pregnancy and lactation

VORICONAZOLE FOR INJECTION can cause foetal harm when administered to pregnantwomen. 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 foetus. VORICONAZOLE FOR INJECTION must not be used during pregnancy unless the benefits to the mother clearly out weight the potential risk to the foetus. Women of child bearing potential should be effective contraception during treatment.

The excretion of VORICONAZOLE FOR INJECTION in breast milk has not been investigated. Breast feeding must be stopped on initiation of treatment with VORICONAZOLE FOR INJECTION

4.7.Fertility, pregnancy and lactation

Please refer to 4.6.

4.8.Effects on ability to drive and use machines

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

4.9. Undesirable Effects

The most commonly reported adverse effects with VORICONAZOLE FOR INJECTION were visual disturbances (including altered/ enhanced visual percentage, blurred vision, blurred color vision change photophobia chromatopsia) eye hemorrhage, chills, fever, headache, abdominal pain, chest pain, sepsis, hypertension, vasodilation, nausea, vomiting, elevated diarrhea, cholestic jaundice, dry mouth, jaundice chills, gastroenteritis, thrombocytopenia anemia (including macrocytic microcytic normocytic megaloblastic aplastic) leukemia, pancytopenia purpura, increased alkaines phoophates, increased hepatic enzymes, increased SGOT, increased SGPT, hypokalemia, peripheral edema, hypomagnesemia, bilurubinemia, increased creatinine, hypoglycemia, respiratory disorder, anxiety, tremor, agiation, paresthesia, rash, purtius, maculopapular rash, photo sensitivity, skin reaction, alopecia exfoliative dermatitis, abnormal kidney function, acute kidney failure, hematuria, thrombocytosis, phlebitis, injection site reactor inflammation and fur syndrome.

4.10. Overdose

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

The minimum lethal oral dose in mice and rats was 300 mg/kg (equivalent to 4 and 7 times the recommended maintenance dose (RMD), based on body surface area). At this dose, clinical signs observed in both mice and rats included salivation, mydriasis, titubation (loss of balance while moving), depressed behavior, prostration, partially closed eyes, and dyspnea. Other signs in mice were convulsions, corneal opacification and swollen abdomen.

5. Pharmacological properties

5.1. Pharmacodynamic properties

VORICONAZOLE FOR INJECTION is a broad spectrum, triazole antifungal agent.

Mechanism of Action

The primary mode of action of VORICONAZOLE FOR INJECTION is inhabitation of fungal cytochrome P450- mediated 14 alpha-lansoterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of alpha-methu sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of VORICONAZOLE FOR INJECTION. It is shown to be more selective for fungal cytochrome? 450 enzymes than for various mammalian cytochrome P 450 enzymes systems.

In vitro, VORICONAZOLE FOR INJECTION displays broad spectrum antifungal activity with antifungal potency against candida species (including fluconazole resistant C.kruseai and resistant strains of C.glabrata and C.albicans) and fungicidal activity against all aspergillus specious tested. In addition, VORICONAZOLE FOR INJECTION shows in vitro fungicidal activity against emerging fungal pathogens, including those such as Scedosporium of Fusarium which havelimited susceptibility to existing antifungal agents.

Clinical efficacy (with partial or complete response) has been demonstrated for

Aspergillus spp. Including A.flavus, A.fumigatus, A.terreus, A.niger, A.nidukans, Candida spp., including C.albicans and limited numbers of C.dubliniensis, C.glabrata, C.inconspicua, C.krusei, C.parapsilosis, C.tropicalis and C.guilliermondii, Sceodosporium spp,, including S.apiospermum, S prolificans and Fusarium spp.

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

In vitro activity against clinical isolates have be observed for Acremonium spp., Alternaria spp., Bipolaris spp., Cladophialophora spp., Histoplasma capsulatum, with most strains being inhibited by interactions of VORICONAZOLE FOR INJECTION in the range of 0.05 to 2µg/mL.

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

5.2.Pharmacokinetic properties

The pharmacokinetic properties of VORICONAZOLE FOR INJECTION are similar following administration by the intravenous and oral routes in healthy subjects. The pharmacokinetics of VORICONAZOLE FOR INJECTION is non linear due to saturation of its metabolism. The inter individual variability of VORICONAZOLE FOR INJECTION pharmacokinetics is high. Greater than proportion increase in exposure is observed with increasing dose.

In vitro activity against clinical isolates has been on observed for *Acremonium spp., Alternaria spp.,* but the clinical significance is unknown: *Curvularia spp. and Sporothrix spp*.

When the recommended intravenous or oral loading dose regimens are administered to

healthy subjects, peak plasma concentration 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 through plasma concentration with VORICONAZOLE FOR INJECTION being achieved by 6 in the majority of subjects. Steady state through plasma concentrations with VORICONAZOLE FOR INJECTION are achieved after approximately 5days of oral or intravenous dosing without a loading dose regimen. However, when an intravenous loading dose regimen is used, steady states through plasma concentrations are achieved within one day.

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

The volume of distribution of steady state of VORICONAZOLE FOR INJECTION 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 200mg or 300mg (approximate range 0.9-15mg/mL) varying degree of hepatic and renal insufficiency do not affect the protein binding of VORICONAZOLE FOR INJECTION.

In vitro studies showed that VORICONAZOLE FOR INJECTION 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 FOR INJECTION. This enzyme exhibits polymorphism. For example 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and blacks the prevalence of poor metabolizers are 3-5% studies conducted in Caucasian and Japanese healthy subject have shown that poor metabolizers 4 fold higher VORICONAZOLE FOR INJECTION exposure(AUC) then their homozygous extensive metabolizer counter parts. Subjects who are heterozygous extensive

metabolizers have no average 2 fold higher VORICONAZOLE FOR INJECTION exposures than their homozygous extensive metabolizer counter parts.

The major metabolite of VORICONAZOLE FOR INJECTION is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma since this metabolite has minimal antifungal activity it does not contribute to the overall efficacy of VORICONAZOLE FORINJECTION.

VORICONAZOLE FOR INJECTION is eliminated via hepatic metabolism with less 2% of the dose excreted unchanged in the urine. After administration of single radiolabelled dose of either oral or IV VORICONAZOLE FOR INJECTION 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 excreted in the first 96hours after both oral and intravenous dosing. The terminal half life of VORICONAZOLE FOR INJECTION is approximately 6hours at 200mg (orally) as a result of nonlinear pharmacokinetics, the terminal half life of VORICONAZOLE FOR INJECTION is dose dependent and therefore not useful in prediction the accumulation of elimination of VORICONAZOLE FOR INJECTION.

In oral multiple dose study, the mean C_{max} and AUC in healthy elderly males (≥65years) were 61% and 86% higher, respectively than in young in males (18-45years) no significant differences in the mean C_{max} and AUC were observed between healthy elderly females (≥65years) and healthy young females (18-45) years. The safety profile of VORICONAZOLE FOR INJECTION in youngand elderly subjects was similar.

After a single oral dose (200mg) of VORICONAZOLE FOR INJECTION in patients with (Child- Pugh class A and patients with moderate (Child–Pugh class b) hepatic insufficiency the mean systemic exposure (AUC) was 3.2 fold higher than controls with normal hepatic function. There was no difference in mean peak plasma concentration (C_{max}) between the groups, in oral dose study ,AUC was similar in subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100mg twice daily compared to subject with normal hepatic function given the standard 200mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were

20% lower in the hepatically impaired group.

It is recommended that the standard loading dose regimens be used out that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving VORICONAZOLE FOR INJECTION. No pharmacokinetic data are available for patients with server hepatic cirrhosis (Child-Pugh class C).

In a single over dose (200Mg) study and in a multiple dose study of I.V VORICONAZOLE FOR INJECTION in subject with normal renal function and mild to severe renal impairment systemic exposure (AUC) and peak plasma concentration (C_{max}) of VORICONAZOLE FOR INJECTION were not significantly affected by renal impairment. Therefore no adjustments are necessary for oral dosing in patients with mild so severe renal impairment.

However, in patients with moderate renal dysfunction k (creatinine clearance 30-50mL/ Min) accumulation of the intravenous vehicle, hydroxypropyl beta cyclodextrin (HPBCD), occurs the mean systemic exposure(AUC) and peak plasma concentration (C_{max}) of HPBCD were increased by 4 fold and almost 50% respectively in the moderately impaired group compared to the normal control group.

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that VORICONAZOLE FOR INJECTION is dialyzed with clearance of 121mL/Min. The intravenous vehicle HPBCD is haemodialysed with a clearance of 55mL/Min.

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. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

6. Pharmaceutical particulars

6.1. List of excipients

Hydroxypropyl beta-cyclodextrin USP, Hydrochloric acid may have been used to adjust pH.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

18 months

6.4. Special precautions for storage

Store below 30° C and protect from moisture.

6.5. Nature and contents of container

Glass Vials: 1's vials

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with localrequirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1. Name and Address of Manufacturer

ASPIRO PHARMA LTD

Survey No. 321, Biotech

Park,Phase-III, Karkapatla,

Markook Mandal,
Siddipet District -
502281,Telangana.

7.2.Name and Address of Principal

Aspiro Pharma Limited, Survey No. 321, Biotech Park,Phase-III, Karkapatla, Markook Mandal, Siddipet District - 502281,Telangana,
India.

8. Registration Number

TAN 21 HM 0107

9. Date of Publication

29th March, 2021

10.Date of revision of text