VORICONAZOLE - CHW

DRUG PROTOCOL©

CHANGE SUMMARY

- Due for mandatory review – no changes made.

READ ACKNOWLEDGEMENT

- Medical prescribing Voriconazole should read and acknowledge this document.
- Nursing administering Voriconazole and Pharmacy staff to be aware of this document

Approved by:	CHW Drug Committee	
Date Effective:	1st July 2014	**Review Period**: 3 year
Team Leader:	Antimicrobial Stewardship Pharmacist	**Area/Dept**: Antimicrobial Stewardship Program

Date of Publishing: 15 July 2014 4:01 PM Date of Printing: 15 July 2014

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Introduction / Background

Voriconazole is a triazole antifungal with broad activity against many types of yeast, moulds including most *Aspergillus spp*. but not the zygomycete fungi.

Registered Use

Invasive aspergillosis, serious candida infections, serious fungal infections caused by Scedosporium spp. and Fusarium spp., other serious fungal infections in patients intolerant of, or refractory to other therapy. Voriconazole is TGA approved for invasive fungal infection (IFI) prophylaxis in haematopoietic stem cell transplantation[1, 2].

Proposed Indications

- Invasive aspergillosis (IA);
    - Invasive infections due to *Scedosporium spp.* and *Fusarium spp*.
      (Note that in *Scedosporium prolificans* infections, a combination of terbinafine and voriconazole should be considered for synergy);
- Organ-localised probable fungal infections where diagnostic studies have failed to identify the aetiologic agent, and zygomycete infection is unlikely.
- Prophylaxis of IFI in haematopoietic stem cell transplant patients

Voriconazole lacks activity against the zygomycete moulds and should only be used if they have been adequately excluded. In invasive paranasal sinusitis, amphotericin compounds are preferred pending laboratory identification of the causative agent.

Several in vitro studies demonstrate antagonism between voriconazole and amphotericin, and there are no persuasive human data supporting the combination of voriconazole with echinocandin drugs. Combination therapy is rarely justified.

Specific patient groups most likely to benefit

- Immunocompromised

Contraindications

Co-administration is contraindicated with rifampicin, carbamazepine, phenobarbitone, sirolimus, and other agents (see full Product Information).

Precautions

Intravenous voriconazole should not be given in patients with moderate to severe renal impairment (CrCl < 50mL/min). The intravenous voriconazole vehicle (cyclodextrin) may accumulate causing hallucinations, hypoglycaemia, electrolyte disturbances and pneumonitis. It is recommended that voriconazole is given orally in these patients.

Dose reduction is required in mild-moderate cirrhosis (See Product Information). Caution is required in patients with azole hypersensitivity, risk factors for cardiac arrhythmia, QT interval prolongation, children < 2 years, or galactose intolerance/ malabsorption.

Voriconazole has many drug interactions including cyclophosphamide, anthracyclines, vinca alkaloids, cyclosporin, tacrolimus, oral anticoagulants, sulfonylureas, statins, benzodiazepines, phenytoin, rifabutin, omeprazole, and HIV medications. See full Product Information and references for additional details.

Dose

Pharmacokinetic data suggest that paediatric patients have increased clearance and require higher doses compared to adult populations. The following dose recommendations reflect the recent literature that supersedes the dose recommendations in the Product Information[3, 4].

The dose of voriconazole should be calculated using the actual body weight in non-obese patients. For obese patients with BMI's > 30, adult pharmacokinetic data suggests ideal body weight should be used to calculate the dose[5-7].

<table>
<tr><th>Age</th><th>Intravenous Therapy</th><th>Oral Therapy</th></tr>
<tr><td>Children under 2 years</td><td colspan="2"><u>Oral / IV:</u> 2 - 4 mg/kg/dose every 12 hours (8-10)
There is limited data available for the safety or dosing of voriconazole in children less than 2 years of age, and there are theoretical concerns regarding permanent retinotoxicity if used in neonates.</td></tr>
<tr><td>2 – 12 years</td><td><u>Load</u>: 9 mg/kg/dose q12h (2 doses)
<u>Maintenance</u>: 8 mg/kg/dose q12h</td><td>9 mg/kg/dose q12h
(Maximum 350mg/dose)</td></tr>
<tr><td rowspan="2">> 12 years</td><td><u>< 50 kg:</u>
Use dose for 2-12 years</td><td><u>< 50 kg:</u>
9 mg/kg/dose q12h
(Maximum 350mg/dose)
(No loading or maintenance)</td></tr>
<tr><td><u>> 50 kg:</u>
<u>Load</u>: 6 mg/kg/dose q12h (2 dose)
<u>Maintenance</u>: 4 mg/kg/dose q12h</td><td><u>> 50 kg:</u>
<u>Load</u>:400 mg/dose q12h (2 doses)
(NOT per kg)
<u>Maintenance:</u> 200 mg/dose q12h
(NOT per kg)</td></tr>
<tr><td colspan="3">Serum voriconazole levels should be monitored after 72hrs and doses adjusted accordingly if levels are not therapeutic</td></tr>
<tr><td colspan="3">There is not maximum dose for intravenous therapy. The maximum oral dose of 350 mg/dose refer the starting dose. Subsequent doses are based on levels.</td></tr>
</table>

Duration of Treatment

The duration of therapy depends on the indication and host immune status. A minimum of 6-12 weeks of therapy is often required for initial therapy of invasive aspergillosis. Patients with ongoing immunosuppression often receive secondary suppressive ("maintenance") therapy.

Duration of voriconazole for prophylaxis is highly dependent on duration of neutropenia, immunosuppressant regime, graft-vs.-host disease, mucositis or previous history of IFI.

Monitoring/Therapeutic range:

Sample timing - Trough level monitoring (just before next dose)

Serum trough level is recommended **at least 72hrs** after commencement of therapy to ensure therapeutic adequacy and avoid toxicity and thereafter monthly re-assay is recommended.

Recommended dose adjustments: [3, 11]

Recommended range:	**1 – 5.5 mg/L**	
Trough level	**Intravenous**	**Oral**
<1 mg/L	↑ 1 mg/kg/dose	↑ 50 mg/dose
>5.5 mg/L (with no adverse effects)	↓ 1 mg/kg/dose	↓ 50 mg/dose
>5.5 mg/L (with adverse effects) **Or** >10 mg/L	Withhold one dose and reduce subsequent doses by 50%	

If adverse effects occur at the 4 – 5.5 mg/L (e.g. elevated LFTs or visual changes) a dose reduction should be made to produce a small reduction in serum level while still maintaining effective antifungal therapy. The dose need not be altered if concentrations are in this range (4 - 5.5 mg/L) and clinical signs of toxicity are not present.

The voriconazole assay is performed Monday, Tuesday and Thursday each week at St. Vincent's Hospital. Voriconazole results are available before 10am the next day (analysis occurs overnight). Call laboratory for voriconazole results on (02) 8382 9184/9185 and a report can be faxed to you immediately.

As the pharmacokinetics of voriconazole in children and adolescents are extremely variable, therapeutic serum level management can often be difficult. In these circumstances, more sophisticated individualised pharmacokinetic studies are available for difficult to stabilise or critically ill patients.

Contact the Antimicrobial Stewardship team for information (page no: 6658 (Pharmacist), 7092 (consultant)).

Safety and adverse effects:

In the largest paediatric series abnormal LFT's were reported in 14%, rash in 14%, visual changes in 5% and photosensitivity in 5%[12].

Monitor renal and hepatic function and electrolytes.

Authorised Prescribers

Voriconazole is a **RED agent** and antimicrobial stewardship approval is **always required**. (page no: 7092) during working hours. Please refer to ABS 4 Kids for further information. http://chw.schn.health.nsw.gov.au/o/groups/drug_therapy/resources/abs4kids/

Place in therapy in relation to alternatives

Voriconazole is the preferred agent for invasive aspergillosis on the basis of RCT data[13]. For most yeast infections, and for refractory febrile neutropenia, other agents are preferred due to ease of administration, reliable therapeutic level achievement, reduced toxicity, lower cost, or lack of interactions. Most candida infections are effectively treated with fluconazole. Fluconazole resistant *Candida spp* may also be resistant to voriconazole. Amphotericin compounds or caspofungin are preferred for initial treatment of candidaemia in patients who have been on azoles. Fluconazole or amphotericin compounds are preferred for neutropenic patients with refractory fever in whom empiric antifungals are indicated.

Administration route/formulations:

IV injection: 200mg/vial

Oral:

Tablets: 200mg, 50mg;

Suspension: 40mg/mL

References:

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