**MONOGRAPH**

**Voriconazole Monograph - Paediatric**

<table>
<thead>
<tr>
<th>Scope (Staff):</th>
<th>Medical, Nursing, Pharmacy</th>
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<td>Scope (Area):</td>
<td>Perth Children’s Hospital (PCH)</td>
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This document should be read in conjunction with this DISCLAIMER

**DESCRIPTION**

- Voriconazole is an anti-fungal agent, it inhibits the synthesis of ergosterol in fungal cell membrane formation.1-3
- Voriconazole is used in the treatment of invasive aspergillosis, especially in immunocompromised patients; and in the treatment of other invasive fungal infections in patients intolerant of, or refractory to other antifungal therapy.1

**INDICATIONS AND RESTRICTIONS**

**IV and Oral: Category B: Monitored**

- If the use is consistent with a standard approved indication, this must be communicated by documenting that indication on all prescriptions (inpatient and outpatient).
- The ChAMP team will review if ongoing therapy is required and/or if the order does not meet ChAMP Standard Indications.
- If use is not for a standard approved indication, phone approval must be obtained from ChAMP before prescribing.

**Standard Indications:**

- Aspergillosis – treatment of proven or probable invasive infection
- Prophylaxis - antifungal, high risk of mould infection

**CONTRAINDICATIONS**

- Hypersensitivity to voriconazole or any component of the formulation.1-3
- Concomitant use of carbamazepine, CYP3A4 substrates (terfenadine, astemizole, cisapride, pimozide, or quinidine), high-dose ritonavir (400 mg every 12 hours), ergot alkaloids, long-acting barbiturates, rifabutin, rifampin, sirolimus, or St John's wort.1,3

**PRECAUTIONS**

- Voriconazole has been shown to prolong the QT interval.3
- Electrolyte disturbances (ie, potassium, magnesium, calcium) increase risk of arrhythmia and QT-interval prolongation and should be corrected prior to and during therapy.2
- Because of the visual side effects, it should be used with caution in children who are unable to have their vision assessed.
Diabetes - oral liquid contains sucrose 0.54 g/mL.¹
Sodium restriction - injection contains 217.6 mg sodium per 200 mg voriconazole.¹

**FORMULATIONS**

- **IV**: 200mg powder for injection vial
- **Oral**: 50mg and 200mg tablet
- 40mg/mL oral powder for reconstitution

**DOSAGE**

The doses listed below fall within the standard range. Higher doses may be prescribed for certain situations in consultation with Infectious Diseases or Microbiology consultants.

*Inter and within-patient variability is significant and therefore therapeutic drug monitoring is essential.*

**Loading dose (IV):**

- Children > 14 years: 6mg/kg/dose (to a maximum of 400mg) 12 hourly for 2 doses.
- Children 12 to 14 years and > 50kg: 6mg/kg/dose (to a maximum of 400mg) 12 hourly for 2 doses.
- Children 2 to 14 years and ≤ 50kg: 9mg/kg/dose (to a maximum of 400mg) 12 hourly for 2 doses.¹

**Maintenance dose (IV):**

- Children > 14 years: 4mg/kg/dose 12 hourly.
- Children 12 to 14 years and > 50kg: 4mg/kg/dose 12 hourly.
- Children 2 to 14 years and ≤ 50kg: 8mg/kg/dose 12 hourly.¹

**Maintenance dose (oral)** Note: oral bioavailability is reduced in children.

*Children > 14 years:*

- Weight > 40kg, 200-300mg twice daily.
- Weight ≤ 40kg 100-150mg twice daily.

*Children 12 to 14 years and > 50kg: 200-300mg twice daily.

*Children 2 to 14 years and ≤ 50kg: 9mg/kg/dose (to a maximum of 350mg) 12 hourly.¹*

- Initial oral maintenance dose should be based on previous IV dose in discussion with Infectious Diseases or Microbiology.
- Subsequent doses should be adjusted based on therapeutic drug monitoring in conjunction with Infectious Diseases, Microbiology or Clinical Pharmacists.¹,²

**Prophylaxis (oral):**

*Initial dose*: Initial prophylaxis use 8mg/kg (to a maximum of 200mg) orally twice daily.
Future doses should be adjusted in 50mg steps based on therapeutic drug monitoring.¹,²

**Neonates:**

- Not routinely used in neonates, contact Infectious Disease or Microbiology consultants for advice

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<tr>
<th>DOSAGE ADJUSTMENT</th>
<th><strong>Dosage adjustment required in renal impairment:</strong></th>
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<td>- The intravenous formulation should be avoided in cases of impaired renal function (with creatinine clearance of less than 50mL/min) as accumulation of the intravenous vehicle SBECID occurs.</td>
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<td>- Consider use of oral formulation or alternative agent if voriconazole is required in patients with impaired renal function.¹,³</td>
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<th>DOSAGE ADJUSTMENT</th>
<th><strong>Dosage adjustment required in hepatic impairment:</strong></th>
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<td>- Dosage adjustment is required in patients with mild to moderate hepatic impairment. Limited information is available on dosage adjustment. Contact Pharmacy for advice.¹,³</td>
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<th>DOSAGE ADJUSTMENT</th>
<th><strong>Additional requirements:</strong></th>
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<td>- Dosing adjustment required for patients on concurrent efavirenz or phenytoin therapy.¹</td>
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<th>RECONSTITUTION</th>
<th><strong>IV:</strong></th>
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<tr>
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<td>- Reconstitute 200mg vial with 19mL of water for injection and shake well.</td>
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<td>- Dilute with compatible fluid to obtain a final concentration of between 0.5 and 5mg/mL.³</td>
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<td>- Discard vial if the vacuum does not draw the solution into the vial.⁴,⁵</td>
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<th>RECONSTITUTION</th>
<th><strong>Oral liquid:</strong></th>
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<td>- Reconstitute with 46mL of water as follows; tap the bottle to release the powder, add 46mL of water to the bottle, shake the closed bottle vigorously for about one minute, remove child resistant cap.</td>
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<td>- Press bottle adaptor into the neck of the bottle and replace cap.</td>
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<td>- The reconstituted solution should be stored at room temperature and discarded after 14 days.³</td>
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<th>ADMINISTRATION</th>
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<tr>
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<td>- Administer at a <strong>maximum rate</strong> of 3mg/kg/hour which is usually over 1 to 2 hours.¹⁻⁶</td>
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<th>ADMINISTRATION</th>
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<td>- Take voriconazole either 1 hour before or 1 hour after food.¹</td>
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| **MONITORING** | Measure trough voriconazole levels 5 days after initiation and 5 days after changes in maintenance doses of both oral and intravenous therapy until target concentrations are achieved.  
**Target trough level is 1 - 6 mg/L**\(^1,7,8\)  
- Once target levels have been achieved, therapeutic drug monitoring should be conducted monthly.  
- More frequent testing should be conducted if there is a change in clinical conditions or concurrent administered medications.  
- Renal and hepatic function should be measured at baseline and weekly throughout treatment.  
- Vision should be assessed regularly if treatment extends beyond 28 days\(^1,4\) |
| **ADVERSE EFFECTS** | Common: reversible visual changes, injection site reactions, infusion reactions (including anaphylaxis), hypotension, skin reactions (photosensitivity, increased incidence of carcinoma with long term treatment), thrombocytopenia, anaemia, hypokalaemia, confusion, paraesthesia, peripheral oedema, pulmonary oedema, respiratory distress syndrome, fever; taste disturbance (oral liquid)\(^1\)  
Rare: periostitis, fluorosis (both with long-term treatment), prolonged QT interval, torsades de pointes, renal tubular necrosis, lymphadenopathy, neurological effects (which may be concentration-dependent), including hallucinations, acute renal failure, arrhythmias and pancreatitis.\(^1\) |
| **COMPATIBLE FLUIDS** | • Glucose 5%  
• Sodium chloride 0.9% and 0.45%  
• Glucose/saline solutions  
• Hartmann’s |
| **STORAGE** | • **Tablets**: Store below 30°C.3  
• **Oral Suspension**: Store powder for suspension at 2 to 8°C. Store reconstituted suspension below 30 °C – discard after 14 days.3  
• **Vial**: Store below 30 °C.3,5  
• **Reconstituted IV solution**: Stable for 24 hours at 2 to 8 °C. Only use clear solutions.5  
• **Diluted IV solution**: Stable for 24 hours at 2 to 8 °C.\(^5\) |
Voriconazole has a number of clinically significant drug interactions. Please contact Pharmacy or refer to literature for further advice.¹,³,⁶

- Voriconazole should be avoided wherever possible in patients also requiring vincristine and other vinca alkaloids and used with caution in patients undergoing therapy with cyclophosphamide or ifosfamide.
- A change in anti-fungal agent for the duration of cyclophosphamide or ifosfamide administration, or a change or delay in the chemotherapy dose may be required.¹

**Please note: The information contained in this guideline is to assist with the preparation and administration of voriconazole. Any variations to the doses recommended should be clarified with the prescriber prior to administration**

**Related internal policies, procedures and guidelines**

- Antimicrobial Stewardship Policy
- ChAMP Empiric Guidelines

**References**

3. MIMS Australia Pty Ltd. MIMS [online]. St Leonards (NSW): CMPMedica Australia Pty Ltd; accessed online 27th April 2017.
8. Walsh, T.J. et al. Pharmacokinetics, Safety, and Tolerability of Voriconazole in
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Immunocompromised Children. Antimicrobial Agents and Chemotherapy 2010 54 (10) pg.4116.

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<td>Children’s Antimicrobial Management Program Pharmacist</td>
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