MONOGRAPH

Voriconazole Monograph - Paediatric

Scope (Staff):	Medical, Pharmacy, Nursing
Scope (Area):	All Clinical Areas

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

⚠ HIGH RISK MEDICINE ⚠

DRUG CLASS

Azole anti-fungal[1, 2]

Voriconazole is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

Voriconazole is indicated in the treatment of invasive aspergillosis and other serious fungal infections with susceptible fungi. It is also used for fungal prophylaxis in high-risk patients.[2-4]

Oral: Monitored (orange) Antifungal

- If the use is consistent with a standard approved indication, this must be communicated to ChAMP 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.

CONTRAINDICATIONS

- Hypersensitivity to voriconazole, other azole antifungals or any component of the formulation.[5, 6]

PRECAUTIONS

- Voriconazole has a number of significant drug interactions. Care should be taken before using any medications that are inducers, substrates or inhibitors of CYP3A4..[2, 5]
- Voriconazole has been shown to prolong the QT interval; use with caution in patients with pro-arrhythmic conditions or with medications that also prolong QT interval.[2, 3, 5]
- Electrolyte disturbances (i.e. potassium, magnesium, calcium) increase risk of arrhythmia and QT-interval prolongation and should be corrected prior to and during therapy.[6]
- Due to the risk of visual side effects, voriconazole should be used with caution in children who are unable to have their vision assessed, especially in courses longer than 28 days.[5]
- Diabetes - oral liquid contains sucrose 0.54 g/mL.[4, 6]
- The IV formulation of voriconazole has a significant sodium content which varies with the different brands. Care should be taken in patients with sodium restriction (approximately 200 mg sodium per 200 mg of voriconazole).[2, 7]
- Oral bioavailability is variably reduced in children. Critically ill children should be treated with intravenous therapy initially and only transition to oral therapy on clinical improvement.[1, 3]
- Patients should be counselled to avoid sun exposure, wear broad rim hats, protective clothing and using a high SPF sunscreen.[3, 5, 6]

FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

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

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Inter and within-patient variability is significant and therefore therapeutic drug monitoring is essential.[5]

Bioequivalence between the oral tablets and suspension has not been demonstrated. Higher doses are likely to be required for patients < 15 years and < 50 kg.[5, 6]

Neonates: There is limited information regarding use of voriconazole in neonates. Discuss use with Infectious Diseases or Clinical Microbiology.

- IV doses of 12-20 mg/kg/DAY in 2 or 3 divided doses have been used.[6]

IV Treatment:

Children ≥ 4 weeks to < 2 years old:	**Initial dose:** 9 mg/kg/dose 12 hourly. With subsequent doses adjusted based on therapeutic drug monitoring. If doses > 40 mg/kg/DAY are required, consider using 8 hourly dosing.[5, 6]	
Children ≥ 2 years to < 12 years old:	**Initial dose (IV load):** 9 mg/kg/dose 12 hourly for two doses only on day one.[1, 3, 6]	**Maintenance dose:** 8 mg/kg/dose given 12 hourly.[1, 3, 6]
Adolescents ≥ 12 years and < 15 years AND < 50kg:	**Initial dose (IV load):** 9 mg/kg/dose 12 hourly for two doses only on day one.[1, 3, 6]	**Maintenance dose:** 8 mg/kg/dose given 12 hourly.[1, 3]
Adolescents ≥ 12 years and < 15 years AND ≥ 50kg:	**Initial dose (IV load):** 6 mg/kg/dose 12 hourly for two doses only on day one.[1, 3, 6]	**Maintenance dose:** 4 mg/kg/dose 12 hourly. The dose may be reduced to 3 mg/kg/dose given 12 hourly if not tolerated. [1, 3, 6]
Adolescents ≥ 15 years:	**Initial dose (IV load):** 6 mg/kg/dose 12 hourly for two doses only on day one.[1, 3]	**Maintenance dose:** 4 mg/kg/dose 12 hourly. The dose may be reduced to 3 mg/kg/dose given 12 hourly if not tolerated. [1, 3]

Oral treatment and prophylaxis:

- Infants and children < 12 years should receive the oral suspension as there may be differences in the absorption of tablets due to shortened gastric transit time.[4]
- Bioequivalence between the oral tablets and suspension has not been demonstrated. Higher doses are likely to be required for patients < 15 years and < 50kg.[5, 6]

Children ≥ 4 weeks to < 2 years old:	Initial dose of 9 mg/kg/dose 12 hourly. With subsequent doses adjusted based on therapeutic drug monitoring. If doses > 40 mg/kg/DAY are required, consider using 8 hourly dosing.[5, 6]
Children ≥ 2 years to < 12 years old:	9 mg/kg/dose (to a maximum initial dose of 350 mg) 12 hourly.[1, 3]
Adolescents ≥ 12 years and < 15years AND < 50kg:	9 mg/kg/dose (to a maximum of 350 mg) 12 hourly.[1, 3, 6]

Adolescents ≥ 12 years and < 15years AND ≥ 50 kg:	**Initial dose (oral load):** 400 mg 12 hourly for two doses.[1, 3, 6]	**Maintenance dose:**200 mg twice daily.[2, 6]
Adolescents ≥15 years AND <40 kg:	**Initial dose (oral load):** 200 mg 12 hourly for two doses.[1, 3, 6]	**Maintenance dose:** 100 mg twice daily. The dose may be increased to 150 mg twice daily based on therapeutic drug monitoring.[2, 6]
Adolescents ≥ 15 years AND ≥ 40 kg:	**Initial dose (oral load):** 400 mg 12 hourly for two doses.[1, 3, 6]	**Maintenance dose:** 200 mg twice daily. The dose may be increased to 300 mg twice daily based on therapeutic drug monitoring [2, 6]

- 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 Pharmacist.
- If inadequate response or the patient is unable to tolerate prescribed doses, the dose should be adjusted in 1 mg/kg/dose increments for IV therapy and voriconazole oral suspension OR 50 mg increments for tablets.[6]
- In patients < 12 years of age who are unable to achieve target levels with the tablet formulation, consider switching to the oral suspension as there may be differences in the absorption of the tablets due to reduced gastric transit time.[6]

Dosing in Overweight and Obese Children: Voriconazole should initially be dosed on ideal body weight with subsequent dosing based on therapeutic drug monitoring.[8, 9]

Renal impairment:

eGFR calculator

- The intravenous formulation of voriconazole should be used with caution in cases of impaired renal function (with creatinine clearance of less than 50 mL/minute/1.73m^2) as accumulation of the intravenous vehicle sulfobutyl ether beta cyclodextrin sodium (SBECD) or hydroxypropylbetadex (HPBCD) occurs.[2, 3, 5, 7]
- Consider use of an oral formulation or an alternative agent if voriconazole is required in patients with impaired renal function.[7]
- There are no paediatric specific dose recommendations in paediatric patients. It is unlikely that any dose adjustments are required.[2, 6]

Hepatic impairment:

- There are no paediatric specific dose recommendations in paediatric patients. In adults, the following recommendations are made:
    - Mild to moderate impairment (Child-Pugh class A or B) use the standard initial dose then reduce maintenance dose by 50%.[5, 6, 10]

- Severe impairment (Child-Pugh class C) use only if benefits outweigh risks. Patients should be closely monitored for toxicity.[5, 6, 10]

Dose adjustment required based on therapeutic drug monitoring:

- Voriconazole has non-linear pharmacokinetics and any dose adjustments should be done with caution.[5]
- If inadequate response or patient is unable to tolerate prescribed doses the dose should be adjusted in 1 mg/kg/dose increments for IV therapy and voriconazole oral suspension OR 50 mg increments for tablets.[3, 6]

RECONSTITUTION & ADMINISTRATION

IV

- Reconstitute 200 mg vial with 19 mL of water for injection to obtain a concentration of 10 mg/mL and shake well.[3, 5, 7]
- Dilute with compatible fluid to obtain a final concentration of between 0.5 and 5 mg/mL.[3, 5, 7, 10]
- Discard vial if the vacuum does not draw the solution into the vial.[7]
- Administer at a **maximum rate** of 3 mg/kg/hour which is usually over 1 to 2 hours.[3-7, 10]

Oral suspension:

- Reconstitute the oral suspension as per the product information with water as follows:
  - Tap bottle until all powder flows freely; add the total volume of water for reconstitution and shake vigorously to suspend powder.
  - Press bottle adaptor into the neck of the bottle and replace cap.
  - Store reconstituted solution at less than 30°C and discard any remaining suspension after 14 days.[4, 5]

Administration:

- Take oral voriconazole either 1 hour before or 1 hour after food.[1, 2, 5, 6]
- Oral bioavailability may be reduced in children.[2]

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids:

- Glucose 5%
- Sodium chloride 0.9% and 0.45%
- Glucose/sodium chloride 0.9% solutions
- Hartmann's[7, 10]

Compatible at Y-site:

Compatibilities of IV drugs must be checked when two or more drugs are given concurrently.

INCOMPATIBLE drugs:

- Voriconazole is INCOMPATIBLE with sodium bicarbonate 4.2% and parenteral nutrition.[2, 7]

- IV voriconazole must not be administered at the same time as blood products or electrolytes, even if separate lines are being used.[2, 7]

MONITORING

- Measure trough voriconazole levels 5 to 7 days after initiation and 5 to 7 days after dose changes of both oral and intravenous therapy until target concentrations are achieved.[6, 11]

Collection tube:

- Serum, no gel (RED), minimum volume 0.5 mL.[12]
- Sample should be sent chilled.[12]

Target trough level is 1 - 6 mg/L[6, 12]

- Once target levels have been achieved, therapeutic drug monitoring should be conducted at least monthly. More frequent testing should be conducted if there is a change in clinical conditions or concurrent administered medications.
- Significant hepatotoxicity and neurotoxicity have been observed when a high voriconazole trough concentration is sustained.[11]
- Renal function should be measured at baseline and regularly throughout treatment.[2, 5]
- Hepatic function should be measured at baseline and weekly for the first month of treatment. If no abnormalities are noted, frequency may be reduced to monthly thereafter. Paediatric patients are at a higher risk of liver enzyme abnormalities.[2, 5]
- Vision should be assessed regularly if treatment extends beyond 28 days.[6]
- Voriconazole should be ceased if there are signs or symptoms of fluorosis or periostitis.[6]
- Significant interpatient variability exists with different population groups. 15-20% of Asians and 3-5% of Caucasians and African Americans may be poor metabolisers of CYP2C19.[5, 6]

ADVERSE EFFECTS

Common: injection site reactions, elevated liver function tests, visual changes (including altered visual perception, blurred vision, colour changes or photophobia – likely dose related and reversible), infusion reactions (including anaphylactoid reactions, fever, flushing, sweating, dyspnoea, nausea, itch and rash), hypotension, skin reactions (photosensitivity, itch, urticaria, severe cutaneous adverse reactions [SCAR's] increased incidence of melanoma or carcinoma with long term treatment and sunlight exposure), hypokalaemia, confusion, paraesthesia, peripheral oedema, pulmonary oedema, respiratory distress syndrome, fever, taste disturbance.[2, 3]

Infrequent: acute renal failure, arrythmias, pancreatitis.[2, 3]

Rare: periostitis, fluorosis, prolonged QT interval, torsades de pointes, renal tubular necrosis, lymphadenopathy, neurological effects (which may be concentration-dependent, including hallucinations), nail changes.[2, 3]

STORAGE

Oral:

- **Tablets:** Store below 30°[4]
- **Oral Suspension**: Store powder for suspension at 2 to 8°C.[4] Store the reconstituted suspension below 30 °C and discard after 14 days.[4]

IV:

- **Vial:** Store below 30°C.[4, 7]
- **Products prepared by Pharmacy Compounding Service (PCS)** store between 2 to 8°C.[7]

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

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 CAHS internal policies, procedures and guidelines

Antimicrobial Stewardship Policy

ChAMP Empiric Guidelines and Monographs

KEMH Neonatal Medication Protocols

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