MONOGRAPH

Flucytosine 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

QUICKLINKS

Dosage/Dosage Adjustments	Administration	Compatibility	Monitoring

DRUG CLASS

Antifungal agent[1]

Flucytosine is also known as 5-FC or 5-fluorocytosine.[1, 2]

INDICATIONS AND RESTRICTIONS

Flucytosine is indicated in the treatment of cryptococcal infections, Candida meningitis and Candida endocarditis in combination with another antifungal.[3, 4]

IV: Restricted (red) antifungal

ChAMP approval is required prior to prescription.

Special Access Scheme restrictions also apply. SAS application/notification must be completed online in accordance with the TGA regulations.

CONTRAINDICATIONS

- Hypersensitivity to flucytosine or any component of the formulation.[4]
- Flucytosine is contraindicated in patients with a history of hypersensitivity to flucytosine or any component of the preparation.
- Contraindicated in those with complete dihydropyrimidine dehydrogenase (DPD) deficiency due to increased risk of severe or fatal toxicity as DPD is a key enzyme involved in the metabolism of 5-fluorouracil, a metabolite of flucytosine.[1, 4-6] Pre-treatment testing for DPD deficiency is not required however, if drug toxicity is confirmed or suspected, testing of DPD activity and withdrawal of treatment should be considered.[1, 4-6]

PRECAUTIONS

- Renal impairment can increase the risk of haematological toxicity; use with extreme caution dosage adjustments are required.[4]
- Concurrent treatment with nephrotoxic agents can reduce the excretion of flucytosine and increase the risk of toxicity, use with caution and monitor flucytosine serum concentration, blood count and renal function.[1]
- There is an increased risk of serious blood dyscrasia in patients with bone marrow suppression, those currently taking myelosuppressive medications, patients undergoing radiation therapy or patients with advanced HIV infection – use with extreme caution. Careful monitoring of hepatic function and the haematopoietic system is required as this may be irreversible.[4, 5, 7]
- Each 250 mL vial contains approximately 34 mmol of sodium.[2]

FORMULATIONS

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

- 2.5 g/250 mL solution for infusion vial (SAS)
- 500 mg tablets (SAS)

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Neonates: Refer to Neonatal Medication Protocols

Flucytosine should always be used in conjunction with another antifungal agent to prevent resistance.[1]

Children > 4 weeks to 18 years:

IV and oral:

- **Standard dose:** 25 mg/kg/dose given 6 hourly. Dose may be increased to 37.5-50 mg/kg/dose given 6 hourly.[1, 4, 5] The lower dose may be sufficient for sensitive organisms.[5]

Renal impairment:

- eGFR calculator
- Dosage adjustment may be required in cases of impaired renal function (with creatinine clearance of less than 40 mL/min).
- CrCl ≥ 40 mL/minute: normal dosing
- CrCl 20 to 40 mL/minute: 100% of the normal dose given 12 hourly
- CrCl 10 to 20 mL/minute: 100% of the normal dose given 24 hourly[1, 5]
- CrCl < 10 mL/minute: 100% of the normal dose given 24 to 48 hourly – future doses should be based on plasma concentrations.[5]

Hepatic impairment:

- No dose adjustment required in hepatic impairment, use with caution and monitor liver function.[6]

ADMINISTRATION

IV infusion:

- Infuse undiluted over 20 to 40 minutes. A longer duration may be used in fluid restricted patients.[1, 2, 5]

Oral:

- Tablets should be taken with food to reduce stomach upset. If multiple tablets are required for each dose, they should be given over a period of 15 minutes to reduce stomach upset.[4, 7]

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids:

- Glucose 5%
- Sodium Chloride 0.9%
- Glucose 4% with Sodium Chloride 0.18%[2]

Compatible at Y-site:

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

MONITORING

General Therapeutic Drug Monitoring

- Monitoring of flucytosine levels is essential in all patients, especially in patients with renal impairment due to the increased risk of bone marrow suppression.[1, 4]
- Initial peak and trough levels should be taken 3-5 days after commencing therapy or any dose change. Once the dose is within the therapeutic range, weekly trough levels are required for ongoing monitoring.[7]

- Peak levels should be taken 2 hours after an oral dose. Trough levels should be taken immediately prior to the next dose.[7]
- Trough levels should be maintained between 25 and 50 mg/L with levels above 25 mg/L required for efficacy.[1, 4, 6]
- Recommended peak levels are 30 - 80 mg/L. Toxicity, including bone marrow toxicity, is associated with peak levels of more than 100 mg/L.[1, 4, 6]

Collection tubes:

- Serum, no gel (RED) or Lithium heparin no gel (DKGNLITH)[8]

Minimum volume required: 2mL[8]

Additional Monitoring:

- At a minimum, renal, hepatic and haematological monitoring is required at baseline, and regularly throughout therapy. Monitoring should be done daily initially and then at least twice weekly.[1, 5, 6]

ADVERSE EFFECTS

Common: anaemia, leucopenia, thrombocytopaenia (risk increased with plasma concentrations of more than 100 mg/L), diarrhoea, nausea, vomiting, elevated liver enzymes (dose related), rash.[1, 5]

Infrequent or Rare: headache, sedation, vertigo, hepatic necrosis, agranulocytosis, gastrointestinal haemorrhage, allergic reactions, toxic epidermal necrolysis, seizures, confusion, hallucinations, cardiotoxicity, aplastic anaemia, confusion, ventricular dysfunction.[1, 5]

STORAGE

- The vials should be stored between 15˚C and 25 ˚C. At temperatures greater than 25˚C, flucytosine is converted to 5-fluorouracil (a cytotoxic) and at temperatures below 15˚C, it may precipitate.[1, 2]
- The tablets should be stored at 25˚C preferably (allowed range 15˚C to 30˚C) and kept protected from light.[6]

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 **flucytosine**. 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

References

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