Pyrimethamine
Newborn use only

2022

Alert	
Indication	Toxoplasmosis
Action	Pyrimethamine is an inhibitor of the enzyme dihydrofolate reductase (DHFR). It blocks the reduction of dihydrofolic acid to tetrahydrofolic acid, leading to disruption of protein synthesis and nuclear division. The affinity of pyrimethamine for protozoal DHFR is much greater than that for the mammalian enzyme. Sulphonamides act synergistically with pyrimethamine by arresting the production of dihydrofolic acid from para-aminobenzoic acid. This results in sequential blockade of the folate pathway of *Toxoplasma gondii*. (3)
Drug type	Antiprotozoal
Trade name	Daraprim (Special Access Scheme)
Presentation	Daraprim 25 mg tablets 2 mg/mL oral suspension can be prepared by pharmacy
Dose	**Treatment for Congenital Toxoplasmosis** Anti-toxoplasma therapy is for **12 months** and as follows: (1,2) **Pyrimethamine** First 2 days: 1 mg/kg/dose every 12 hours followed by From Day 3 to 6 months: 1 mg/kg/dose once daily followed by 7th month to 12 months: 1 mg/kg/dose three times a week. **Sulfadiazine** 50 mg/kg/dose every 12 hours from day 1 of treatment to 12 months and, **Calcium folinate (folinic acid)** 10 mg three times a week for 12 months until 1 week following cessation of pyrimethamine treatment.
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – Not applicable. Renal impairment – Limited data. Caution may be required. (3) Hepatic impairment - Caution is required. (3)
Maximum dose	25 mg/dose
Total cumulative dose	-
Route	Oral
Preparation	2 mg/mL oral suspension prepared in-house by pharmacy: A 2 mg/mL oral suspension may be made with tablets and a 1:1 mixture of Simple Syrup, NF and methylcellulose 1%. Crush forty 25 mg tablets in a mortar and reduce to a fine powder. Add small portions of vehicle and mix to a uniform paste; mix while adding the vehicle in incremental proportions to almost 500 mL; transfer to a calibrated bottle, rinse mortar with vehicle, and add a quantity of vehicle sufficient to make 500 mL. Label "shake well" and "refrigerate". Stable for 91 days.(9,10)
Administration	Give with food/feed Pyrimethamine should be given concurrently with sulfadiazine.(3)
Monitoring	Full blood count especially for neutropenia. Monitoring twice weekly is recommended
Contraindications	History of hypersensitivity to pyrimethamine or any of the components of the preparation.
Precautions	Depression of haematopoesis: Can occur in about 25% of patients. All patients receiving pyrimethamine should be given a folate/folinate supplement to reduce the risk of bone marrow depression. (3) Seizures: Caution should be exercised in patients with a history of seizures. Hepatic impairment: Liver is the main route of metabolism. Caution is required. Galactosemia and hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption – Daraprim contains lactose. (3) G6PD deficiency: Use with caution in patients with possible G6PD deficiency.
Drug interactions	Pyrimethamine may further depress folate metabolism in patients receiving treatment with other folate inhibitors or agents associated with myelosuppression, including co-trimoxazole, trimethoprim, zidovudine or cytostatic agents (e.g. methotrexate). (3) The concurrent administration of lorazepam and pyrimethamine may induce hepatotoxicity. Highly protein bound compounds: Pyrimethamine may displace other drugs from protein binding sites, causing elevated concentrations of unbound drugs; this may be of particular clinical concern for drugs that are both highly protein bound and have a narrow therapeutic index. (3)
Adverse reactions	Hematologic: Leucopenia, anaemia, thrombocytopenia, pancytopenia, neutropenia (4,5)

	Nervous system: Headache, dizziness, convulsions (6) Gastrointestinal: Anorexia, glossitis (atrophic), vomiting, diarrhoea Dermatologic: Rash (3)
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Oral suspension: 91 days when stored in the fridge.
Storage	Tablets: store below 30°C. Protect from light. Oral suspension: 2-8°C.
Excipients	Lactose, maize starch, hydrolysed starch, docusate sodium and magnesium stearate.(3)
Special comments	-
Evidence	**Efficacy** Neonates with Congenital Toxoplasmosis: Treatment with the following medications is recommended for 12 months: Pyrimethamine: 1 mg/kg every 12 hours for 2 days followed by 1 mg/kg daily for 6 months followed by the same dose, 3 times a week to complete 12 months; Sulfadiazine: 50 mg/kg every 12 hours; and Folinic acid: 10 mg 3 times a week for 12 months. Folinic acid should be administered until 1 week following cessation of pyrimethamine. (1,2) The United States data suggest that risk of recurrent eye disease is around 31% in infants with CT who had received 12 months of postnatal treatment during their first year of life. (7) The French cohort study showed the risk of recurrence of eye disease within 12 years after the diagnosis of the first eye lesion was around 34%. The French cohort had mothers who were treated during pregnancy and infants who were also postnatally treated. (8) Older children (diagnosed beyond neonatal age) with active disease (Chorioretinitis): (1) Treatment is given for at least 1–2 weeks after resolution of all signs and symptoms of acute chorioretinitis (with sharpening of the lesion borders and/or scarring of the lesion) and for ~4–6 weeks total. Acute eye disease often resolves within 10 to 14 days after initiation of treatment, but there are cases that take a longer time to resolve. Pyrimethamine First 2 days: 1 mg/kg/dose orally twice a day (maximum 50 mg/day) Then: 1 mg/kg/dose orally once daily (maximum 25 mg/day) Sulfadiazine 75 mg/kg/dose orally × 1, followed by 50 mg/kg/dose orally twice a day Folinic acid 10–20 mg orally three times a week Prednisone (severe chorioretinitis) 0.5 mg/kg/dose twice a day (maximum 40 mg/day; rapid taper) **Pharmacokinetics** It is 87% protein bound. The main route of metabolism is in liver. Plasma half-life is 80-90 hours. Kidney is not the major route of excretion and excretion is not significantly altered in renal failure. (3) Plasma concentration of pyrimethamine were measured in 24 infants aged 1–5 months, treated for congenital toxoplasmosis. Pyrimethamine was used in a single daily dose of 0.35–0.98 mg/kg daily. Concentration of pyrimethamine ranged from 0.01 to 1.2 µg/mL. In 14 children, concentration achieved therapeutic value. In 7 patients, concentration was below therapeutic level, and in 3 patients above therapeutic level. Transient moderate neutropenia was noted in 46% of infants. Modification of therapy was necessary in 12 patients. (11) ANMF consensus: Routine monitoring of plasma concentrations is not practised in Australia. **Safety** Pyrimethamine/sulfadiazine treatment in children was associated with adverse events in 14%-50%.(4,5) Main adverse effect was neutropenia, more often with higher doses and especially when folinic acid was not administered. Seizures have been reported with pyrimethamine overdose. (6)
Practice points	
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