PRODUCT INFORMATION

DARAPRIM TABLETS

NAME OF MEDICINE: Pyrimethamine

DESCRIPTION:
The chemical name of pyrimethamine is 5-(4-Chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, with a molecular formula C$_{12}$H$_{13}$ClN$_{4}$ and a molecular weight of 248.7. It is practically insoluble in water; slightly soluble in ethanol and dilute HCl. The chemical structure is:

![Chemical Structure of Pyrimethamine]

CAS NUMBER – 58-14-0

ACTIONS:

Pharmacology:
Pyrimethamine is an inhibitor of the enzyme dihydrofolate reductase (DHFR). It blocks the reduction of dihydrofolic acid to tetrahydrofolic acid which is an essential coenzyme in the production of nucleic acids, thereby 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 production of dihydrofolic acid from para-aminobenzoic acid. This results in sequential blockade of the folate pathway of Toxoplasma which, in contrast to man, is unable to utilise preformed folate.

Pharmacokinetics:
Peak plasma levels are found between 2 and 4 hours after oral administration of a 100 mg dose of pyrimethamine and the plasma half-life is approximately 90 hours. 87% of pyrimethamine is bound to plasma proteins and its pKa is 7.34.

Pyrimethamine is secreted in breast milk (and may be of some value in the protection of breastfed infants from malaria).
INDICATIONS:

Toxoplasmosis: Daraprim in combination with a sulphonamide is effective in the treatment of congenital and acquired infections.

CONTRAINDICATIONS:

Daraprim should not be given to individuals with a history of pyrimethamine sensitivity or any of the components of the preparation.

PRECAUTIONS:

In the treatment of toxoplasmosis, all patients receiving Daraprim should be given a folate supplement to reduce the risk of bone marrow depression. Whenever possible calcium folinate, 6 mg daily, should be administered; or alternatively folic acid, 5 mg daily, should be given. Full blood counts should be carried out weekly during therapy and for a further 2 weeks after treatment is stopped. Should signs of folate deficiency develop treatment must be discontinued and high doses of calcium folinate administered.

Daraprim may exacerbate folate deficiency in subjects predisposed to this condition through disease or malnutrition. Accordingly, a folinic acid supplement should be given to such individuals. In patients with megaloblastic anaemia due to folate deficiency the risks versus benefits of administering Daraprim require careful consideration.

Caution should be exercised in administering Daraprim to patients with a history of seizures; large loading doses should be avoided in such patients (See Adverse Reactions Section).

When a sulphonamide is given an adequate fluid intake should be ensured to minimise the risk of crystalluria.

Since pyrimethamine is administered with a sulphonamide for the conditions indicated the general precautions applicable to sulphonamides should be observed.

Use in renal impairment:

The kidney is not the major route of excretion of pyrimethamine and excretion is not significantly altered in patients with renal failure. There are, however, no substantial data on the use of Daraprim in renally impaired subjects. Since Daraprim is co-administered with a sulphonamide, care should be taken to avoid accumulation of the sulphonamide in renally impaired patients.

Use in hepatic impairment:

Data on the use of pyrimethamine in patients with liver disease are limited. Daraprim in combination with sulphonamides has been used effectively to treat toxoplasmosis in a patient with mild hepatic disease. There are no general recommendations for dosage reductions for liver-impaired states but consideration should be given to dose adjustments for individual cases.
Use in pregnancy: (Category B3):
Pyrimethamine may interfere with folic acid metabolism and animal experiments have shown that administration of very high doses of pyrimethamine during organ development may give rise to birth defects typical of folic acid antagonism. If pyrimethamine is given during pregnancy, folic acid supplementation may be required.
Pyrimethamine in combination with sulphonamide has been used for many years in the treatment of toxoplasmosis during pregnancy. Both these infections carry a high risk to the foetus. Pyrimethamine crosses the placenta and, although there is a theoretical risk of foetal abnormalities from all folate inhibitors given during pregnancy, there have been no reports that have shown with any certainty that pyrimethamine is associated with human teratogenicity. Nevertheless, caution should be exercised in the administration of pyrimethamine.

Consideration should be given to the treatment of all suspected cases of acquired toxoplasmosis in pregnancy. The risks associated with the administration of Daraprim must be balanced against the dangers of abortion or foetal malformation due to the infection. Toxoplasmosis is thought not to infect the foetus before the sixth week of pregnancy and only rarely during early placentation.

Treatment is indicated only for:

1. Women whose serological tests become positive during pregnancy.
2. Women who show rising titres of antibodies against Toxoplasma during pregnancy.

Although the eyes are sometimes affected during an acute acquired attack, most authorities consider that ocular toxoplasmosis is usually a late manifestation of congenital infection. Thus, in the majority of cases, maternal ocular disease does not reflect a danger to the foetus. Pregnant women should only be treated in the presence of rising titres or if the eye lesion threatens maternal vision.

Treatment during pregnancy is indicated in the presence of confirmed placental or foetal infection or when the mother is at risk of serious sequelae. However, in view of the theoretical risk of foetal abnormality arising from the use of Daraprim in early pregnancy, its use in combination therapy should be restricted to the second and third trimesters. Alternative therapy is therefore advised in the early stages of pregnancy.

Concurrent administration of folinic acid is advocated when pyrimethamine is used for the treatment of toxoplasmosis during pregnancy.

Use in Lactation:
Pyrimethamine enters human breast milk. In view of the high doses of pyrimethamine and concurrent sulphonamides needed in toxoplasmosis treatment, breast feeding should be avoided for the duration of treatment.

Interactions:
Daraprim by its mode of action, may further depress folate metabolism in patients receiving treatment with other folate inhibitors, or agents associated with myelosuppression, including co-trimoxazole, trimethoprim, proguanil, zidovudine, or cytostatic agents (eg. methotrexate).

Occasional reports suggest that individuals taking pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should a trimethoprim/sulphonamide combination be prescribed concurrently.

The concurrent administration of lorazepam and pyrimethamine may induce hepatotoxicity.
Daraprim may cause exacerbation of the myelosuppressive effects of cytostatic agents, especially those of the antifolate methotrexate.

Convulsions have occurred after concurrent administration of methotrexate and pyrimethamine to children with CNS leukaemia and cases of fatal bone marrow aplasia have been associated with the administration of daunorubicin, cytosine arabinoside and pyrimethamine to individuals suffering from acute myeloid leukaemia. Also, seizures have occasionally been reported when pyrimethamine was used in combination with antimalarial drugs.

*In vitro* data suggest that antacid salts and the anti-diarrhoeal agent kaolin reduce the absorption of pyrimethamine.

The high protein binding exhibited by pyrimethamine may prevent protein binding by other compounds. This will be of relevance when the level of unbound, concomitantly administered drug (e.g., quinine or warfarin) affects its efficacy or toxicity.

**ADVERSE EFFECTS:**

Since a concurrent sulphonamide is to be taken with pyrimethamine for the indications listed, the relevant prescribing information for the sulphonamide should be consulted for sulphonamide-associated adverse events.

At the recommended dose, side effects are rare. Occasionally, rashes have been observed which disappeared when administration of Daraprim was stopped.

There have been rare instances of pneumonia with cellular and eosinophilic pulmonary infiltration when pyrimethamine was taken once weekly in association with sulfadoxine.

Therapeutic doses of Daraprim have been shown to depress haematopoiesis in about 25% of patients. The likelihood of anaemia or thrombocytopenia developing is reduced by concurrent administration of calcium folinate.

Nausea, colic, vomiting and diarrhoea are common during early treatment. They seldom necessitate withholding treatment.

Less common side-effects are headache, giddiness, dryness of mouth or throat, fever, malaise, depression, rash and other skin disorders, including dermatitis and abnormal skin pigmentation.

There have been isolated reports of hyperphenylalaninaemia in neonates treated for congenital toxoplasmosis.

Circulatory collapse and buccal ulceration have been reported in association with Daraprim but only in patients treated with doses higher than those recommended.

Precipitation of a grand mal attack in one patient predisposed to epilepsy has been reported but the clinical significance has not been defined.

Convulsions were reported very rarely, predominantly in patients treated for toxoplasmosis. Pancytopenia, responsive to folate treatment, has been reported very rarely in patients with probable pre-existing folate deficiency. Fatalities have occurred in the absence of folate treatment.
DOSAGE AND ADMINISTRATION:

Toxoplasmosis: Daraprim should be given concurrently with sulphadiazine or other sulphonamides.

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<thead>
<tr>
<th></th>
<th>Daraprim</th>
<th>Sulphadiazine</th>
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<tbody>
<tr>
<td></td>
<td>Initial Dose</td>
<td>subsequent daily dose (daily in 4 divided doses)</td>
</tr>
<tr>
<td>Adults and children over 6 years</td>
<td>2 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Children 2-6 years</td>
<td>1 tablet</td>
<td>½ tablet</td>
</tr>
<tr>
<td>Children 10 months - 2 years</td>
<td>-</td>
<td>½ tablet</td>
</tr>
<tr>
<td>Infants 3-9 months</td>
<td>-</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>Infants under 3 months</td>
<td>-</td>
<td>¼ tablet on alternate days</td>
</tr>
</tbody>
</table>

150 mg/kg bodyweight (maximum 4 g)

150 mg/kg bodyweight (maximum 2 g)

150 mg/kg bodyweight (maximum 1.5g)

100 mg/kg bodyweight (maximum 1g)

100 mg/kg bodyweight (maximum 750 mg)

Treatment should be given for 3 to 6 weeks. If further therapy is indicated, a period of 2 weeks should elapse between treatments.

OVERDOSAGE:

Symptoms and signs:

Vomiting and convulsions occur in cases of severe, acute overdoses. Ataxia, tremor and respiratory depression can also occur.

Chronic excess doses can result in bone marrow depression (eg. megaloblastic anaemia, leucopenia, thrombocytopenia) resulting from folic acid deficiency.

Treatment:

Adequate fluids should be given to ensure optimal diuresis. Routine supportive treatment including maintenance of a clear airway and control of convulsions should be given. To counteract possible folate deficiency, calcium folinate (9 to 15 mg by intramuscular injection every 6 hours) should be given until signs of toxicity have subsided.
There may a delay of 7 to 10 days before the full leucopenic side effects become evident, therefore calcium folinate therapy should be continued for the period at risk.

PRESENTATION AND STORAGE CONDITIONS:

White, round, biconvex tablets. The obverse side is scored in the middle, with GS and A3A imprinted above and below the score mark respectively. The reverse side is plain.

Each tablet contains pyrimethamine 25mg as the active ingredient plus the inactive ingredients: lactose, maize starch, hydrolysed starch, docusate sodium and magnesium stearate.

Daraprim tablets are packed in either foil or blister* packs of 50 tablets.

(*: Blister pack not currently available)

Store below 30°C. Protect from light.

NAME AND ADDRESS OF SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

POISON SCHEDULE: S4

DATE OF APPROVAL:
Date of last safety-related notification: 26 November 2003
Date of last amendment: 24 November 04

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