SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Daraprim 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of pyrimethamine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Each tablet is white and round with the marking GS A3A.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of:

Toxoplasmosis, including ocular infections, proven foetal infection following maternal infection during pregnancy, and toxoplasmosis in immune-deficient patients (for the treatment of toxoplasmosis Daraprim must always be used in combination with a synergistic agent e.g. sulphadiazine).

Treatment is not normally required for asymtomatic or mild toxoplasma infection.

4.2 Posology and method of administration

Posology

Toxoplasmosis (including ocular infections)

Daraprim should be given concurrently with sulphadiazine or another appropriate antibiotic.

In the treatment of toxoplasmosis, all patients receiving Daraprim should be given a folinic acid supplement (calcium folinate) to reduce the risk of bone marrow depression (see section 4.4).

Daraprim treatment should generally be given for 3 to 6 weeks and not less than six weeks in immunosuppressed patients. If further therapy is indicated, a period of two weeks should elapse between treatments.

There have been no dose response studies of pyrimethamine in the treatment of toxoplasmosis. The following recommendations are therefore for guidance only.

Adults

A loading dose of Daraprim 100 mg should be given for the first 1 to 2 days, followed by 25 mg to 50 mg daily. This should be given together with 2 g to 4 g of sulphadiazine daily in divided doses.

- Foetal toxoplasmosis during pregnancy

  Daraprim 50 mg every 12 hours for 2 days, followed by 50 mg daily. This should be given together with an initial dose of sulfadiazine 75 mg/kg, followed by 50 mg/kg every 12 hours (to a maximum of 4 g daily) (see section 4.4 and section 4.6).

Immune-deficient adults and adolescents

Guidelines for the treatment of opportunistic infections in HIV-infected adults and adolescents consider pyrimethamine plus sulfadiazine to be the initial therapy of choice for *Toxoplasma gondii* encephalitis and recommend the following doses, based on body-weight, be given for at least 6 weeks:

– less than 60 kg - pyrimethamine 200 mg orally, followed by 50 mg daily plus sulfadiazine 1 g orally every 6 hours

– 60 kg or more - pyrimethamine 200 mg orally, followed by 75 mg daily plus sulfadiazine 1.5 g orally every 6 hours.

Paediatric Population

Children over 6 years

A loading dose of Daraprim 100 mg should be given for the first 1 to 2 days, followed by 25 mg to 50 mg daily. This should be given together with 2 g to 4 g of sulphadiazine daily in divided doses.

Children aged 5 to 6 years

An initial dose of Daraprim 2 mg/kg bodyweight (to a maximum of 50 mg) followed by 1 mg/kg bodyweight/day (to a maximum of 25 mg); combined with sulphadiazine 150 mg/kg bodyweight (maximum 2 g) daily in four divided doses.

Children under 5 years

There is insufficient data to provide specific dose recommendations. This formulation is not suitable for children under 5 years.

Immune-deficient children

Dosage regimens for immune-deficient children are not defined.

Elderly

There is no definitive information on the effect of Daraprim on elderly individuals. It is theoretically possible that elderly patients might be more susceptible to folate depression associated with the daily administration of Daraprim in the treatment of toxoplasmosis, and supplementation of folinic acid is therefore essential (see section 4.2).

Patients with renal impairment

Daraprim should be given with caution to patients with renal impairment. Since Daraprim is co-administered with a sulphonamide care should be taken to avoid accumulation of the sulphonamide in patients with renal impairment (see section 4.4).

Patients with hepatic impairment

Daraprim should be given with caution to patients with hepatic impairment. There are no general recommendations for dosage reductions for liver-impaired states but consideration should be given to dose adjustments for individual cases (see section 4.4).

Method of administration

For oral administration.

4.3 Contraindications

Daraprim is contraindicated in:

Hypersensitivity to pyrimethamine or to any of the excipients of this medicinal product.

Daraprim should not generally be used during the first trimester of pregnancy (see section 4.6).

Since Daraprim is to be taken in conjunction with another drug for the indications listed, the relevant prescribing information for the synergistic agent should also be considered.

Breast-feeding should be avoided during toxoplasmosis treatment. (See section 4.6).

4.4 Special warnings and precautions for use

Depression of haematopoesis

Daily therapeutic doses of Daraprim have been shown to depress haematopoesis in 25% to 50% of patients. The likelihood of inducing leucopenia, anaemia or thrombocytopenia is reduced by concurrent administration of calcium folinate. Pancytopenia, responsive to folate, has been reported in patients with probable pre-existing folate deficiency. Fatalities have occurred in the absence of folate treatment.

Prevention of haematological toxicity

During pregnancy and in other conditions predisposing to folate deficiency, a folate supplement should be given. The co-administration of a folate supplement is necessary for treatment of toxoplasmosis (see section 4.2). Full blood counts should be carried out weekly during therapy and for a further two weeks after treatment is stopped. In immunosuppressed patients, full blood counts should be carried out twice weekly. Should signs of folate deficiency develop, treatment must be discontinued and high doses of calcium folinate administered. Calcium folinate should be used because folic acid does not correct folate deficiency due to dihydrofolate reductase inhibitors.

Daraprim may exacerbate folate deficiency in subjects predisposed to this condition through disease or malnutrition. Accordingly, a calcium folinate 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.

Seizures

Caution should be exercised in administering Daraprim to patients with a history of seizures; large loading doses should be avoided in such patients (see section 4.8).

Risk of crystalluria

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

Precautions applicable to sulphonamides

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

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 patients with renal impairment, therefore Daraprim should be given with caution. Since Daraprim is co-administered with a sulphonamide, care should be taken to avoid accumulation of the sulphonamide in renally impaired patients.

Hepatic impairment

The liver is the main route for metabolism of pyrimethamine. Data on the use of Daraprim in patients with liver disease are limited. Daraprim should be given with caution to patients with hepatic impairment. There are no general recommendations for dosage reductions for liver-impaired states but consideration should be given to dose adjustment for individual cases.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5. Interactions with other medicinal products and other forms of interaction

Folate inhibitors, agents associated with myelosuppression

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 cotrimoxazole, trimethoprim, proguanil, zidovudine, or cytostatic agents (e.g. methotrexate).

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.

Megaloblastic anaemia has been reported occasionally in individuals who took pyrimethamine concurrently with a trimethoprim/sulphonamide combination.

Methotrexate

Convulsions have occurred after concurrent administration of methotrexate and pyrimethamine to children with central nervous system leukaemia.

Other antimalarial drugs

Seizures have occasionally been reported when pyrimethamine was used in combination with other antimalarial drugs.

Lorazepam

The concurrent administration of lorazepam and Daraprim may induce hepatotoxicity.

Antacid salts, kaolin

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

Highly protein bound compounds

The high protein binding exhibited by pyrimethamine may prevent protein binding by other compounds (eg. quinine or warfarin). This could affect the efficacy or toxicity of the concomitant drug depending on the levels of unbound drug.

4.6 Fertility, pregnancy and lactation

Pregnancy

Daraprim should not be used during the first trimester of pregnancy unless the benefits outweigh the risk. Daraprim has been shown to be teratogenic in *animal* studies. The risks associated with the administration of Daraprim must be balanced against the dangers of abortion or foetal malformation due to the infection.

Treatment with Daraprim and sulfadiazine 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.

Pregnant women receiving Daraprim must be given a concurrent folinic acid supplement.

Breastfeeding

Pyrimethamine enters human breast milk. It has been estimated that over a 9-day period an average weight infant would receive about 45% of the dose ingested by the mother. 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.

Fertility

There are no relevant data available

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Some patients may experience dizziness or convulsions, therefore, caution is recommended (see section 4.8).

4.8 Undesirable 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.

It is important to note that the frequency categories assigned for each adverse event below are only estimates as suitable data for accurately calculating incidence were not available. Adverse events may vary in their incidence according to the indication and the possible contribution of concomitant sulphonamides to the occurrence of these events is unknown. In addition some events may be related to the underlying disease.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:
very common ≥1/10,
common ≥1/100 and <1/10,
uncommon ≥1/1000 and <1/100,
rare ≥1/10,000 and <1/1000,
very rare <1/10,000.

Blood and lymphatic system disorders

Very common: Anaemia
Common: Leucopenia, thromboctopenia
Very rare: Pancytopenia

Nervous system disorders

Very common: Headache
Common: Dizziness
Very rare: Convulsions (see section 4.4 and section 4.7)

Respiratory, thoracic and mediastinal Disorders

Very rare: Pneumonia with cellular and eosinophilic pulmonary infiltration (observed when pyrimethamine was administered once weekly in association with sulfadoxine)

Gastrointestinal disorders

Very common: Vomiting, nausea, diarrhoea
Very rare: Colic, buccal ulceration

Skin and subcutaneous tissue disorders

Very common: Rash
Uncommon: Abnormal skin pigmentation
Very rare: Dermatitis

General disorders and administrative site conditions

Uncommon: Fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or by searching for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Vomiting and convulsions occur in cases of severe, acute overdoses. Ataxia, tremor and respiratory depression can also occur. There have been isolated cases with fatal outcomes following acute overdose of pyrimethamine.

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

Management

Routine supportive treatment, including maintenance of a clear airway and control of convulsions.

Adequate fluids should be given to ensure optimal diuresis.

To counteract possible folate deficiency, calcium folinate 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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pyrimethamine is an antiparasitic agent.

Pharmacotherapeutic group: diaminopyrimidines, ATC code: P01B D01.

Mechanism of Action

The antiparasitic action of pyrimethamine is due to its specific activity on folic acid metabolism in the *Plasmodium* and *Toxoplasma* parasites. In this respect it competitively inhibits the dihydrofolate reductase enzyme with an affinity far greater for the protozoal than for the human enzyme.

5.2 Pharmacokinetic properties

Absorption

Pyrimethamine is almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations generally occur 2 to 4 hours after a dose and can vary widely between individuals; concentrations ranging from 260 to 1411 ng/ml after daily oral doses of 25 mg.

Distribution

The volume of distribution for pyrimethamine is approximately 2L/kg. In patients with HIV infection, population pharmacokinetic analysis has indicated that the mean volume of distribution (corrected for bioavailability) is 246+/-64L.

About 80 to 90% of the pyrimethamine is bound to plasma proteins.

Pyrimethamine is mainly concentrated in the kidneys, lungs, liver, and spleen. In AIDS patients given daily dose of pyrimethamine, concentrations of about one-fifth of those in the serum occur in cerebrospinal fluid.

Pyrimethamine crosses the placenta. It is distributed into breast milk

Elimination

Pyrimethamine is predominantly metabolised by the liver. The mean elimination half-life is 85 hours. Pyrimethamine is slowly excreted in urine. In AIDS patients, the total clearance is 1.28+/-0.41L/h resulting in an elimination half life of 139+/-34h. Data are lacking on the nature of the metabolites of pyrimethamine, their route/rate of formation and elimination in man and any pharmacological activity, particularly after prolonged daily dosing.

Multiple dose studies indicate that steady state is achieved in 12 to 20 days with daily dosing. It is theoretically possible that metabolic pathways might be saturable, leading

to excessive accumulation of the drug in some patients. However, it has been demonstrated that plasma levels are approximately proportional to dose at steady state so this appears unlikely. Genetic variation in the exposure to pyrimethamine has been reported but these data are unsubstantiated.

Some studies in patients with AIDS have indicated shorter half lives than those noted above: these are very likely to be a consequence of inappropriate sampling and analytical techniques. However, if there are patients in whom the half-life is particularly short, steady state therapeutic levels might be inadequate.

5.3 Preclinical safety data

Mutagenicity

In microbial tests, pyrimethamine was found to be non-mutagenic in the Ames Salmonella assay whereas DNA damage was seen in the Escherichia coli repair assay. Further in vitro data indicate that pyrimethamine induces mutagenic activity in mouse lymphoma cells in the absence, but not in the presence of metabolic activation.

Pyrimethamine also showed clastogenic activity in mammalian lymphocytes in the absence of metabolic activation.

Following intraperitoneal administration, pyrimethamine has been shown to induce chromosomal damage in male rodent germ cells although studies in somatic cells (micronucleus tests) are either negative or inconclusive. Studies following oral administration of pyrimethamine in rodents showed negative results in female germ cells and in male and female bone marrow/peripheral blood cells.

Carcinogenicity

A study in mice (dosed with either 500 or 1000 ppm pyrimethamine in the diet for 5 days per week, for 78 weeks) showed no evidence of carcinogenicity in females. Survival in the male mice did not allow for an assessment of carcinogenicity in this sex.

A similar study in rats dosed at 200 or 400 ppm pyrimethamine showed no evidence of carcinogenicity.

Teratogenicity

No changes in early development were seen in embryos from 15 mice given a single intra-gastric dose of pyrimethamine (50 mg/kg bodyweight) on the first day of gestation. However development of mouse and rat embryos in culture was severely hindered by pyrimethamine in a dose-dependent manner.

Pyrimethamine was teratogenic in rodents and in the Gottingen minipig in a dose-dependent manner.

Other studies in rats dosed at either 1 mg/kg or 10 mg/kg bodyweight showed some inhibition of developmental processes but no teratological effects. Pyrimethamine was not teratogenic in rabbits at dose levels up to 100 mg/kg bodyweight/day administered on days 6 to 18 of pregnancy. Pyrimethamine markedly reduced early stage cell division in rabbit embryos but implantation and foetal development were normal.

Fertility

A study in rats dosed with 5 mg/kg bodyweight/day for 6 weeks resulted in reduced sperm concentrations and testis weights, but there were no effects on fertility. Reversible arrest of spermatogenesis was shown in a study on mice dosed with 200 mg/kg/day for 50 days. However, this dose is far in excess of human therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate
Maize Starch
Hydrolysed Starch
Docusate sodium
Magnesium stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C.
Store in the original container.

6.5 Nature and contents of container

PVC/PVdC/aluminium foil blister pack or PVC/PVdC/child-resistant aluminium foil blister pack
Pack size: 30 tablets

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

The Wellcome Foundation Ltd
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

Trading as:
GlaxoSmithKline UK

8. MARKETING AUTHORISATION NUMBER(S)

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