Prescribing Information

PrDARAPRIM® TABLETS

Pyrimethamine, USP

Antimalarial

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Date of Preparation:
December 3, 2012
Date of Revision:

Control Number: 160416

Prescribing Information

PrDARAPRIM®

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Clinical Pharmacology

Pyrimethamine is an antiparasitic agent of the diaminopyrimidine type. It is a folic acid antagonist and the rationale for its therapeutic action is based on the differential requirement between host and parasite for nucleic acid precursors involved in growth. It competitively inhibits the dihydrofolate reductase enzyme with an affinity far greater for the protozoal than for the human enzyme. This activity is highly selective against plasmodia and *Toxoplasma gondii*. Pyrimethamine does not destroy gametocytes, but arrests sporogony in the mosquito.

Pyrimethamine is rapidly absorbed from the gastrointestinal tract after administration. Time to peak plasma concentrations is reached 2 to 4 hours in healthy volunteers. Peak plasma concentrations vary widely between individuals and range from 260 to 1411ng/mL after daily doses of 25mg. Plasma levels of pyrimethamine in patients with AIDS can vary by a factor of four following the same oral dose.

Pyrimethamine has a volume of distribution of about 2.0 L/kg. About 87% of the drug binds to plasma proteins. Pyrimethamine has been shown to reach the cerebrospinal fluid achieving concentrations that were approximately one fifth of those in blood from patients with AIDS given daily doses.

Pyrimethamine is predominantly metabolised by the liver. The mean elimination half-life is 85 hours (ranging from 35-175 hours). Total body clearance can range between 20 and 28ml/hr/kg. Pyrimethamine is slowly excreted in urine; following a single 50mg dose only 23% was recovered from the urine over one week, while 16-32% of a 100mg dose was excreted over 40 days.

Indications and Clinical Use

Treatment of acute malaria: Fast-acting schizonticides (e.g., chloroquine or quinine) are indicated and preferable for the treatment of acute attacks. However, conjoint use of DARAPRIM® (pyrimethamine) will initiate transmission control and suppressive cure.

Treatment of Toxoplasmosis: DARAPRIM® is also indicated for the treatment of toxoplasmosis. For this purpose the drug should be used conjointly with a sulfonamide, since synergism exists with this combination.

Contraindications

DARAPRIM® is contraindicated in patients with a history of hypersensitivity to pyrimethamine or to any component of the preparation.

Precautions

General

The co-administration of a folate supplement is necessary for treatment of toxoplasmosis. 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 folinic acid should be administered; or alternatively, folic acid may be given. Full blood counts should be carried out weekly during therapy and for a further two weeks after treatment is stopped. Should signs of folate deficiency develop, treatment must be discontinued and high doses of folinic acid 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, and Dosage and Administration sections).

When a sulfonamide is given in combination, an adequate fluid intake should be ensured to minimize the risk of crystalluria.

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

The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalarial dosage and approaches the toxic level. If signs of folic acid deficiency develop (see Adverse Reactions) reduce the dosage or discontinue the drug according to the response of the patient. Folinic acid may be administered in a

dosage of 5 to 15mg orally, i.v. or i.m. daily for 3 days, or as required to produce a return of depressed platelet or white blood cell counts to safe levels.

Warn patients to keep pyrimethamine out of the reach of children since accidental ingestion has led to fatality.

Use in Pregnancy

Pyrimethamine in combination with sulphonamide has been used for many years in the treatment of malaria and 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.

Pregnant women receiving DARAPRIM® must be given a concurrent folic acid supplement.

Malaria

At the recommended treatment doses, DARAPRIM® is not contra-indicated during pregnancy.

Toxoplasmosis

When pyrimethamine is used for the treatment of toxoplasmosis, the risks associated with the administration, must be balanced against the danger of abortion or fetal malformation due to the infection.

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.

Pyrimethamine like other folic acid antagonists, may, in large doses produce teratogenic effects in laboratory animals.

In patients receiving high dosage, as for the treatment of toxoplasmosis, full blood counts should be carried out weekly. In patients with convulsive disorders a smaller "starting" dose (for toxoplasmosis) is recommended to avoid the potential nervous system toxicity of pyrimethamine.

Nursing Mothers

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.

Patients with Special Diseases and Conditions

Pyrimethamine should be used with caution in patients with hepatic or renal disorders.

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

The liver is the main route for metabolism of pyrimethamine. 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. DARAPRIM® was also successfully used to treat malaria in two patients who also had concurrent hepatitis infections. There are no general recommendations for dosage reductions for liver-impaired states but consideration should be given to dose adjustments for individual cases.

Pyrimethamine may exacerbate folate deficiency due to innate disease or malnutrition.

Drug Interactions

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

The concurrent administration of lorazepam and pyrimethamine may induce hepatotoxicity.

Pyrimethamine, 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 (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. When used prophylactically, megaloblastic anaemia has been reported occasionally in individuals who took pyrimethamine in excess of 25mg weekly concurrently with a trimethoprim/sulphonamide combination.

Convulsions have occurred after concurrent administration of methotrexate and pyrimethamine to children with leukemia affecting the central nervous system. Also, seizures have occasionally been reported when pyrimethamine was used in combination with other antimalarial drugs.

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

Adverse Reactions

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.

Nausea, colic, vomiting and diarrhea are common during early toxoplasmosis treatment and have also occasionally occurred in association with malaria treatment.

At the 75mg dose used in malaria treatment, disorders of cardiac rhythm and hematuria have occurred which may have been associated to some extent with the nature of the infection.

Insomnia has been reported when pyrimethamine has been given at weekly doses above those recommended.

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

Daily therapeutic doses of DARAPRIM® have been shown to depress hematopoiesis in some 25-50% of patients. The likelihood of inducing leucopenia, anaemia or thrombocytopenia is reduced by concurrent administration of folinic acid.

Pancytopenia responsive to folate treatments, has been reported very rarely in patients with probable pre-existing folate deficiency. Fatalities have occurred in the absence of folate treatment.

Less common side effects are headache, giddiness, dryness of mouth and 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.

Buccal ulceration has been reported in association with DARAPRIM®. Circulatory collapse has also been reported but only in patients treated with higher doses than recommended.

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

Symptoms and Treatment of Overdosage

Symptoms

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.

Other reported symptoms have included cyanosis and tachycardia.

Treatment

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

Adequate fluids should be given to ensure optimal diuresis.

Gastric lavage may be of value only if instituted within 2 hours of ingestion, in view of the rapid absorption of pyrimethamine.

Fresh blood transfusions, to counteract blood dyscrasias should be available.

To counteract possible folate deficiency, folinic acid, 9 to15mg daily should be given until the signs of toxicity have subsided. There may be a delay of 7 to 10 days before the leucopenic side effects become evident; therefore, folinic acid therapy should be continued for the period at risk.

Dosage and Administration

Treatment of Acute Malaria

Use pyrimethamine in areas where only susceptible plasmodia exist. The drug is not recommended alone in the treatment of acute attacks of malaria in nonimmune persons. Fast acting schizonticides (chloroquine or quinine) are indicated for treatment of acute attacks. However, conjoint pyrimethamine dosage of 25mg daily for 2 days will initiate transmission control and suppressive cure.

Should circumstances arise wherein pyrimethamine must be used alone in semi-immune persons, the adult dosage for an acute attack is 50mg daily for 2 days; children 4 to 10 years old may be given 25mg daily for 2 days.

Pyrimethamine should be given concurrently with sulfalene, sulfadoxine or another long-acting sulfonamide.

Adults and Children over 14 Years
As a single dose, 50 to 75mg pyrimethamine with 1 to 1.5g sulfalene or sulfadoxine.

Children 9 to 14 Years
As a single dose, 50mg pyrimethamine with 1g sulfalene or sulfadoxine.

Children 4 to 8 Years
As a single dose, 25mg pyrimethamine with 500mg sulfalene or sulfadoxine.

Children under 4 Years
As a single dose, 12.5mg pyrimethamine with 250mg sulfalene or sulfadoxine.

Treatment of Toxoplasmosis

Pyrimethamine should be given concurrently with sulfadiazine or another appropriate sulfonamide (see Precautions).

Adults and Children over 6 Years
An initial dose of 50mg pyrimethamine followed by 25mg pyrimethamine daily given with 150mg/kg (maximum 4g) sulfadiazine daily in 4 divided doses.

Children 2 to 6 Years
An initial dose of 25mg pyrimethamine followed by 12.5mg pyrimethamine daily given with 150mg/kg (maximum 2g) sulfadiazine daily in 4 divided doses.

Children 10 Months to 2 Years
12.5mg pyrimethamine daily given with 150mg/kg (maximum 1.5g) sulfadiazine daily in 4 divided doses.

Infants 3 to 9 Months
6.25mg pyrimethamine daily given with 100mg/kg (maximum 1g) sulfadiazine daily in 4 divided doses.

Infants under 3 Months
6.25mg pyrimethamine on alternate day given with 100mg/kg (maximum 750mg) sulfadiazine given in 4 divided doses on alternate days.

The risk of administering sulfadiazine or other sulfonamides to neonates should be weighed against their therapeutic benefit.

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

Pharmaceutical Information

Composition

Each white, biconvex DARAPRIM® (pyrimethamine) tablet, with code number DARAPRIM A3A on the same side as the score mark, contains: pyrimethamine USP 25mg.

Also contains cornstarch, lactose and potato starch.

Stability and Storage Recommendations

Store between 15° to 30°C and keep dry.

Availability of Dosage Forms

DARAPRIM® is supplied in bottles of 50 tablets.