NEW ZEALAND DATA SHEET

D-PENAMINE
D-penicillamine Tablets 125 mg, 250 mg

Presentation

D-PENAMINE tablets 125 mg: 8 mm, normal convex, white, film-coated tablet debossed “DS” on one side and “125” on the other. Each tablet contains 125 mg D-penicillamine.

D-PENAMINE tablets 250 mg: 10 mm, normal convex, white, film-coated tablet debossed “DM” on one side and “250” on the other. Each tablet contains 250 mg D-penicillamine.

Indications

Severe, active rheumatoid arthritis.

As a chelating agent in the treatment of Wilson's disease and lead poisoning. D-PENAMINE will enhance the urinary excretion of gold and mercury and other heavy metals.

In the treatment of cystinuria in cases where high-fluid regimens are not adequate, or in conjunction with them.

Dosage and Administration

D-PENAMINE is intended for oral administration in adults. In all patients receiving D-penicillamine, it is important that D-PENAMINE be given on an empty stomach, at least one hour before meals or two hours after meals, and at least one hour apart from any other medicine, food or milk.

Rheumatoid Arthritis

Not more than 250 mg daily for one month, increasing by the same amount at intervals of not less than one month, until a daily dose of 1500 mg has been reached. The dose should be kept to the lowest which is effective in order to minimise side-effects. Many patients respond to a maintenance dose of 750 mg daily, and it may be worthwhile to keep patients on this dosage for several months before deciding on a further increment. There is no pre-determined dose of D-PENAMINE which will suit all patients, and the dose for each individual must be sought by careful monitoring over a period of months. D-penicillamine should be given in divided doses. Therapeutic response to changes in maintenance dosage usually will not become evident for six to eight weeks. Some do not respond despite continued use of full doses. There is little point in persevering with D-PENAMINE if there is no response after six months at a full maintenance dose. Occasionally patients who have responded initially to a particular dose begin to relapse. Most of these will respond to an increase which should be gradual. Both seronegative and seropositive rheumatoid arthritis usually respond to D-PENAMINE.

As a Chelating Agent
Wilson's disease
Most adult patients require the medicine in a daily dose of 1500 mg to 2000 mg. Improvement is often slow, though cupruresis is immediate and there may be clinical deterioration at first. Except in the most advanced case, substantial improvement can generally be expected. Patients who are vomiting or unable to swallow should be given parenteral E.D.T.A.

Lead Poisoning
Patients who are vomiting or who are unable to swallow should be given parenteral E.D.T.A., but all others are best treated by means of D-PENAMINE in an oral dose of 250 to 1000 mg daily, in divided doses.

Other heavy metals poisoning
D-PENAMINE will enhance the urinary excretion of gold, iron, antimony, zinc and mercury.

Cystinuria
A single 500 mg dose on retiring, following free fluids during the day, may effect stone dissolution in a functioning kidney. 750 to 1000 mg daily in divided doses is generally adequate and it should not be necessary to exceed 2000 mg daily.

Children
D-PENAMINE is not recommended for use in children.

Contraindications
Hypersensitivity to D-penicillamine or any of the other ingredients (see List of Excipients).
D-PENAMINE should not be used in patients who are receiving gold therapy or antimalarial drugs.
Agranulocytosis, aplastic anaemia or severe thrombocytopenia due to D-penicillamine.
Lupus erythematosus.
Moderate or severe renal impairment.

Warnings and Precautions
Full blood and platelet counts should be performed and renal function should be assessed prior to treatment with D-penicillamine.

Monitoring of blood and platelet counts should be carried out at appropriate intervals, together with urinalysis for detection of haematuria and proteinuria (see Adverse Effects). Urinalysis should be carried out weekly at first, and following each increase in dose, then monthly, although longer intervals may be adequate for cystinuria and Wilson's disease. Increasing or persistent proteinuria may necessitate withdrawal of therapy.

During the first eight weeks of therapy full blood counts should be carried out weekly or fortnightly and also in the week after any increase in dose, otherwise monthly thereafter. In cystinuria or Wilson's disease, longer intervals may be adequate.

Withdrawal of treatment should be considered if platelets fall below 120,000/mm$^3$ or white blood cells below 2,500/mm$^3$, or if three successive falls are noted within the normal range. Treatment may be restarted at a reduced dose when counts return to normal, but should be permanently...
withdrawn on recurrence of leucopenia or thrombocytopenia. D-penicillamine may potentiate the bone marrow suppression caused by clozapine.

Care should be exercised in patients with renal insufficiency; modification of dosage may be necessary.

Especially careful monitoring is necessary in the elderly since increased toxicity has been observed in this patient population regardless of renal function.

Concomitant use of NSAIDs and other nephrotoxic medicines may increase the risk of renal damage (see Interactions).

D-penicillamine should be used with caution in patients who have had adverse reactions to gold. Concomitant or previous treatment with gold may increase the risk of side effects with D-penicillamine treatment. Therefore D-penicillamine should be used with caution in patients who have previously had adverse reactions to gold and concomitant treatment with gold should be avoided (see Contraindications).

If concomitant oral iron, digoxin or antacid therapy is indicated, this should not be given within two hours of taking D-penicillamine (see Interactions).

Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions (see Adverse Effects).

Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see Adverse Effects).

Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately (see Adverse Effects).

A late rash, described as acquired epidermolysis bullosa and penicillamine dermopathy, may occur after several months or years of therapy. This may necessitate a reduction in dosage (see Adverse Effects).

Breast enlargement has been reported as a rare complication of D-penicillamine therapy in both women and men (see Adverse Effects). Danazol has been used successfully to treat breast enlargement which does not regress on medicine discontinuation.

The use of disease-modifying antirheumatic drugs (DMARDs), including D-penicillamine, has been linked to the development of septic arthritis in patients with rheumatoid arthritis, although rheumatoid arthritis is a stronger predictor for the development of septic arthritis than the use of a DMARD (see Adverse Effects).

Deterioration of the neurological symptoms of Wilson's disease (dystonia, rigidity, tremor, dysarthria) have been reported following introduction of D-penicillamine in patients treated for this condition. This may be a consequence of mobilisation and redistribution of copper from the liver to the brain (see Adverse Effects).

Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since D-penicillamine increases the requirement for this vitamin (see Interactions).

**Use in Pregnancy**
The safety of D-penicillamine for use during pregnancy has not been established (see Preclinical Safety Data).

**Wilson's disease:** There have been several cases of reversible cutis laxa in infants born to mothers taking D-penicillamine throughout pregnancy. Although there have been no controlled studies on the use of D-penicillamine during pregnancy, two retrospective studies have reported the successful delivery of 43 normal infants to 28 women receiving between 500 and 2000 mg of D-penicillamine daily. There are also anecdotal reports both of congenital abnormalities and of successful outcomes in patients who have remained on D-penicillamine during pregnancy. If treatment with D-penicillamine is to be continued following a risk-benefit analysis, consideration should be given to reducing the dose of D-penicillamine to the lowest effective dose.

**Cystinuria:** Whilst normal infants have been delivered, there is one report of a severe connective tissue abnormality in the infant of a mother who received 2000 mg D-penicillamine daily throughout pregnancy. Whenever possible, D-penicillamine should be withheld during pregnancy, but if stones continue to form, the benefit of resuming treatment must be weighed against the possible risk to the foetus.

**Rheumatoid arthritis:** D-penicillamine should not be administered to patients who are pregnant, and therapy should be stopped when pregnancy is diagnosed or suspected, unless considered to be absolutely essential by the physician.

**Use in Lactation**

Due to the lack of data on use in breast feeding patients and the possibility that D-penicillamine may be transmitted to new-borns through breast milk, D-PENAMINE should only be used in breast feeding patients when it is considered absolutely essential by the physician.

**Effects on ability to drive and use machines**

None known.

**Adverse Effects**

The most common of all adverse effects are thrombocytopenia and proteinuria.

Thrombocytopenia occurs commonly. The reaction may occur at any time during treatment and is usually reversible (see Warnings and Precautions).

Proteinuria occurs in up to 30% of patients and is partially dose-related (see Warnings and Precautions).

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1,000$ and $< 1/100$); rare ($\geq 1/10,000$ and $< 1/1,000$); very rare ($< 1/10,000$); not known (where no valid estimate of the incidence has been derived).

NB: The incidence and severity of some of the adverse reactions, noted below, varies according to the dosage and nature of the disease under treatment.

**Table 1**

<table>
<thead>
<tr>
<th>Blood and Lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Not known:</td>
</tr>
<tr>
<td>Neutropenia$^a$, agranulocytosis$^1$, aplastic anaemia$^1$, haemolytic anaemia,</td>
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<tr>
<td>Category</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
</tr>
<tr>
<td>Rare:</td>
</tr>
<tr>
<td>Not known:</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Hepatobiliary disorders</td>
</tr>
<tr>
<td>Immune system disorders</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
</tr>
<tr>
<td>Rare:</td>
</tr>
<tr>
<td>Not known:</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>Not known:</td>
</tr>
</tbody>
</table>


Vascular disorders

| Not known: | Pulmonary haemorrhage |

1. Deaths from agranulocytosis and aplastic anaemia have occurred.

2. Nausea, anorexia, fever and rash may occur early in therapy, especially when full doses are given from the start.

3. Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions (see Warnings and Precautions).

4. Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended (see Warnings and Precautions).

5. Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately (see Warnings and Precautions).

6. A late rash, described as acquired epidermolysis bullosa and penicillamine dermopathy, may occur after several months or years of therapy (see Warnings and Precautions).

7. Breast enlargement has been reported as a rare complication of D-penicillamine therapy in both women and men (see Warnings and Precautions).

8. The reaction may occur at any time during treatment and are usually reversible (see Warnings and Precautions).

The development of septic arthritis in patients with rheumatoid arthritis has been linked to the use of DMARDs, including D-penicillamine (see Warnings and Precautions).

Deterioration of the neurological symptoms of Wilson's disease (dystonia, rigidity, tremor, dysarthria) have been reported following introduction of D-penicillamine in patients treated for this condition (see Warnings and Precautions).

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**Interactions**

Concomitant use of iron or antacids: oral absorption of D-penicillamine may be reduced by concomitant administration of iron or antacids (see Warnings and Precautions).

Concomitant use of digoxin: oral absorption of digoxin may be reduced by concomitant administration of D-penicillamine (see Warnings and Precautions).

Concomitant use of NSAIDs and other nephrotoxic medicines may increase the risk of renal damage (see Warnings and Precautions).

Concomitant use of gold: concomitant use not recommended (see Contraindications).

Concomitant use of clozapine: D-penicillamine may potentiate the blood dyscrasias seen with clozapine (see Warnings and Precautions).

Concomitant use of zinc: oral absorption of D-penicillamine may be reduced by concomitant administration of zinc; absorption of zinc may also be reduced by D-penicillamine.
Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since D-penicillamine increases the requirement for this vitamin (see Warnings and Precautions).

**Overdose**

The treatment of D-penicillamine overdose is nonspecific and essentially supportive. There is no known antidote.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

**Further Information**

D-penicillamine, the D-isomer of 3-mercaptovaline, is a white or practically white crystalline powder, with a slight characteristic odour. It is slightly soluble in alcohol, insoluble in chloroform and ether but freely soluble in water. It is a characteristic degradation product of penicillins. Hydrolysis of penicillin yields only the D-isomer which is used in clinical practice. The D-penicillamine used in D-PENAMINE tablets is prepared in this way, and is supplied as the free amino acid.

**Actions**

Pharmacotherapeutic group: M01C C

It is the stable thiol group that gives D-penicillamine its biological activity, making it an effective chelating agent for heavy metals. This enables it to form a soluble mixed disulphide with cystine and to depolymerise large protein molecules. D-penicillamine will form a chelate with copper. If the sulphhydryl groups of certain enzymes are blocked by copper, the free sulphhydryl group of D-penicillamine may in some way be able to reactivate such enzymes, providing a second mechanism of action in Wilson's disease. D-penicillamine also reduces excess cystine excretion in cystinuria. This is done, at least in part, by disulphide interchange between penicillamine and cystine, resulting in formation of penicillamine-cysteine disulphide, a substance that is much more soluble than cystine and is excreted readily.

It is not known how D-penicillamine acts in producing beneficial effects in rheumatoid arthritis. Known actions which might have a bearing on activity in rheumatoid disease include interference with the immune response, chelation of copper, dissociation of macroglobulins, effect on collagen, and antiviral activity.

**Pharmacokinetics**

D-penicillamine is readily absorbed from the alimentary tract following oral administration. Up to 80% of the absorbed dose is excreted in the urine mainly as penicillamine disulphide or as a mixed disulphide. It appears that distribution of D-penicillamine is through the water space of the body. Plasma protein binding and tissue binding, especially by the skin, delay final clearance by several weeks. The initial half-life in blood is 20 minutes but this phase lasts for less than one hour. The half-life of the stored D-penicillamine is about 90 hours.

**Preclinical Safety Data**

D-penicillamine has been shown to be teratogenic in rats when given in doses several times higher than those recommended for human use.
There is no known LD50 value for D-penicillamine. In studies some rats died after oral administration of 10,000 mg/kg, but intraperitoneal injections of a dose of 660 mg/kg caused no deaths.

Pharmaceutical Precautions

List of Excipients
Glycerol, hypromellose, microcrystalline cellulose, povidone, sodium starch glycolate, stearic acid, titanium dioxide.

D-PENAMINE is gluten, lactose and sugar free.

Special Precautions for Storage
Store at or below 25°C.

Protect from heat and moisture.

Package Quantities

D-PENAMINE Tablets 125 mg: Bottles of 100 tablets
D-PENAMINE Tablets 250 mg: Bottles of 100 tablets

Medicines Classification

Prescription Medicine

Sponsor Details

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Date of Preparation

2 September 2014