D-PENAMINE
D-penicillamine

PRODUCT INFORMATION

Description
D-PENAMINE (D-penicillamine) is the D-isomer of 3-mercaptovaline. It is a characteristic degradation product of penicillins. Hydrolysis of penicillin yields only the D-isomer which is used in clinical practice. Penicillamine is prepared in this way and is supplied as the free amino acid.

D-penicillamine 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.

Pharmacology
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 sulphhydril groups of certain enzymes are blocked by copper, the free sulphhydril 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.

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.

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.
Contraindications

Hypersensitivity to D-penicillamine, except in a life-threatening situation.

D-PENAMINE should not be used in patients who are receiving gold therapy or antimalarial drugs.

Warnings

Physicians planning to use D-PENAMINE should thoroughly familiarise themselves with potential toxicity and benefits. D-PENAMINE should never be used casually. Each patient should remain constantly under the close supervision of the physician. Patients should be warned to promptly report any symptoms suggesting toxicity.

The skin and mucous membranes should be observed for allergic reactions.

The use of D-penicillamine has been associated with fatalities due to aplastic anaemia, agranulocytosis, thrombocytopenia, Goodpasture’s Syndrome and myasthenia gravis.

Because of the potential for serious haematological and renal adverse reactions to occur at any time, haemoglobin determination, white and differential cell count, direct platelet count and urinalysis should be carried out at weekly intervals for the first four weeks, then at two-weekly intervals for the next five months and monthly thereafter for the duration of therapy.

Patients should be instructed to report promptly fever, sore throat, chills, bruising or bleeding.

Some patients may experience drug fever, a marked febrile response to D-penicillamine, usually in the second or third week following initiation of therapy. Drug fever may sometimes be accompanied by a macular cutaneous reaction.

D-PENAMINE treatment should be withdrawn if the total WBC falls below 3000 per cu. mm, neutrophils fall below 2000 or platelets below 120000, or if a steady decline over three successive tests is observed, even though the counts remain within the normal range.

If fever, or a reaction in the skin, blood or urine appears, D-PENAMINE should be discontinued until the reaction subsides. After this, it should be re instituted in patients with Wilson’s disease in a small dose that is gradually increased until full dosage is attained.

Liver function tests are advisable every six months during the first year and a half of therapy.

A nephrotic syndrome may develop during therapy, and proteinuria may be a warning sign of its development. Close observation of patients is essential. In some cases proteinuria disappears with continued therapy; in other cases the drug must be discontinued. When a patient develops proteinuria, the physician should ascertain that it is a symptom of the nephrotic syndrome and not transitory proteinuria unrelated to D-penicillamine. Withdraw treatment if albumin in the urine increases progressively to exceed 2 g per day.

If successive tests demonstrate haematuria discontinue D-PENAMINE treatment immediately.

D-PENAMINE increases the requirement of pyridoxine (Vitamin B6) and in rare cases causes central and peripheral nervous symptoms which could be due to pyridoxine deficiency. Some authorities recommend prophylactic administration of 25mg pyridoxine daily.
When D-PENAMINE is used in cystinuria, an annual X-ray is advised. Cystine stones form rapidly, sometimes in six months.

**Use in Pregnancy (Category D)**

D-Penicillamine can cause cutis laxa in the human foetus. D-PENAMINE should not be given during pregnancy if possible because of its affinity for metals and cystine, and its effect on collagen. In severe, untreated Wilson's disease and when stones continue to form in patients with cystinuria, the benefits of therapy with the drug must be evaluated against the risk. A patient with cystinuria, who was treated with D-penicillamine 2 g a day during pregnancy, gave birth to a child with generalised connective tissue defect that may have been caused by D-penicillamine.

**Use in Lactation**

No information is available on concentration in breast milk.

**Interactions with Other Drugs**

D-penicillamine potentiates isoniazid.

**Precautions**

Cross-allergy to penicillin and D-penicillamine may occur and D-penicillamine should be used with caution in the penicillin-hypersensitive patient.

A neurological examination prior to therapy is advisable to distinguish pre-existing neurological disturbances from any which may arise during treatment. Should neurological abnormalities occur (excluding loss of taste) D-penicillamine should be withdrawn and other appropriate therapy initiated.

Patients being treated with D-penicillamine should not be subjected to elective surgical procedures, especially vascular surgery, as D-penicillamine has the capacity to interfere with collagen cross links. Therapy with D-PENAMINE should, if possible, be discontinued for at least six weeks prior to surgery.

Some patients have experienced reversible optic neuritis, possibly related to pyridoxine deficiency, following the administration of a racemic mixture of penicillamine. However, symptoms of pyridoxine deficiency have not been reported in patients receiving D-penicillamine. Patients complaining of visual disturbances should undergo a full ophthalmological examination.

The frequency and severity of some of the adverse reactions are greatly reduced by gradual introduction of D-PENAMINE.

**Adverse Reactions**

D-penicillamine causes allergic reactions, the most common of which is a maculopapular or erythematous rash early in therapy, and occasionally accompanied by fever, arthralgia or lymphadenopathy. Urticaria has occurred.

Other adverse reactions that have been reported include nephrotic syndrome, hepatic dysfunction, falling hair, tinnitus, elevated sedimentation rate, eosinophilia, monocytosis, leukocytosis, thrombocytosis,
thrombocytopenia, bone marrow hypoplasia, leukopenia, and granulocytopenia ranging in severity from asymptomatic and reversible to agranulocytosis with fatalities. Nausea, loss of appetite, vomiting and occasional diarrhoea may occur. Thrombophlebitis, pancreatitis, cheilosis, glossitis, gingivostomatitis, and elastosis perforans serpiginosa have been reported, but are rare. There may be reversible impairment of taste. A syndrome closely resembling disseminated erythematous has been reported.

Severe and ultimately fatal glomerulonephritis and intra-alveolar haemorrhage (Goodpasture's syndrome) has occurred rarely.

Iron deficiency may develop, especially in menstruating women, and in children, supplemental iron therapy may be required.

It has been reported that D-penicillamine also can induce a pemphigus-like disorder, polymyosis and symptoms similar to those of myasthenia gravis.

There have been a few reports of increased serum alkaline phosphatase, and positive cephalin flocculation and thymol turbidity tests.

Reversible optic neuritis, possibly connected with pyridoxine deficiency, has been reported following administration of a racemic mixture of penicillamine.

D-penicillamine causes an increase in the amount of soluble collagen. In the rat, this results in inhibition of normal healing and also a decrease in tensile strength of intact skin. In man, this same abnormality probably is the cause of increased skin friability at sites especially subject to pressure or trauma, such as knees, shoulders, elbows, toes, and buttocks. Extravasations of blood may occur. These may be purpuric, with external bleeding if the skin is broken, or they may appear as vesicles containing dark blood. Neither type is progressive. There is no apparent association with bleeding elsewhere in the body and no associated coagulation defect has been found. Therapy with D-PENAMINE may be continued in the presence of these lesions, although they may disappear if dosage is reduced.

The chelating action of the drug may cause increased excretion of other heavy metals such as zinc, mercury and gold.

Breast enlargement has been reported as a rare complication of D-penicillamine therapy in both women and men. Breast enlargement may resolve with discontinuation of D-penicillamine. Some patients required an anti-estrogen medication to decrease breast size. In a few patients breast enlargement was considerable and/or prolonged with poor resolution and others required surgery.

**Dosage and Administration**

For oral administration.

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 drug, food or milk.
Rheumatoid disease:

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 drug 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.

Overdosage

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

Tablets DD1069, D-PENAMINE, containing D-penicillamine (base) 125 mg, bottles of 100.

Tablets DD1070, D-PENAMINE, containing D-penicillamine (base) 250 mg, bottles of 100.

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